Total Synthesis of (−)-Nakadomarin A

Total Synthesis of (−)-Nakadomarin A

A thesis presented

by

Bichu Cheng

to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

July 2013

Dissertation Advisor: Professor David A. Evans Bichu Cheng

Total Synthesis of (−)-Nakadomarin A

Abstract

A convergent and scalable total synthesis of polycyclic manzamine alkaloid (−)-nakadomarin A is described.

In the first generation route, a cascade reaction sequence with a Mannich/Pictet-Spengler reaction was devised. A Michael adduct resulting from an enal and malonate addition was obtained. The adduct was then transformed into a bisamide, a potential precursor for the cascade reaction. Attempts of the cascade reaction utilizing the amide failed.

The second generation route features a cascade reaction sequence of a conjugate addition /enamine alkylation /Pictet-Spengler reaction. The requisite macrocyclic amine and unsaturated iminium fragments were prepared. The conjugate addition product was observed in the presence of a base at low temperature. However, the adduct readily underwent a more facile azetidine formation, as opposed to the desired enamine alkylation, and lead to decomposition of the conjugate addition product.

Modifications of both fragments finally lead to a successful cascade reaction (Scheme 1). Unsaturated bicyclic lactam fragment **A** was prepared from acrolein in 5 steps, and macrolactam fragment **B** was prepared from 3-furfural in 7 steps. A double Michael addition reaction (or cyclization) between **A** and **B** provided the desired product **C** in 79% yield and 9:1 dr on more than one-gram scale. Completion of the total synthesis of

(−)-nakadomarin A was then achieved in one or two steps from compound **C**. Over 500 mg of (−)-nakadomarin A has been prepared following this route.

Scheme 1. Total synthesis of (−)-nakadomarin A.

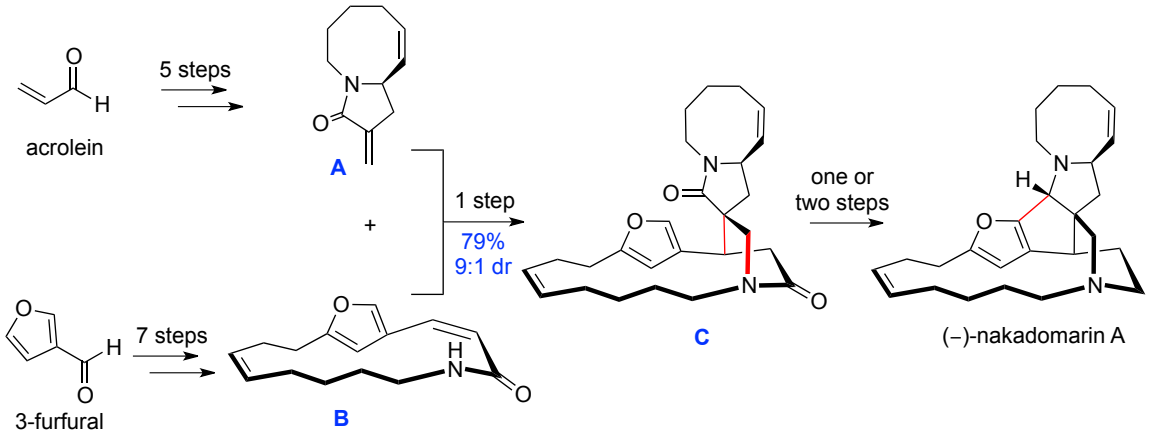


Table of Contents

Acknowledgements

It has been really lucky for me to study abroad at Harvard. It is such a great place to learn and to be educated.

First of all, I want to thank my advisor Professor David Evans for his support and advice over the years. Both his criticism and encouragement helped me grow up to be a synthetic organic chemist. Dave has very high standard of excellence, as well as deep insight in organic chemistry, I wish I could keep a little bit of each in my own future career.

Professor Eric Jacobsen and Professor Andrew Myers are gratefully acknowledged for serving on my graduate advisory committee and thesis defense committee.

I would like to thank my collaborators Simone, Yimon, Andrew and Joseph for their help on the project. I really appreciate their patience and persistence on attacking the problems. I also want to thank SusAnn, Art and Shunming for proofreading this thesis.

Finally, I would like to thank my parents and siblings for their continuous support in my everyday life.

List of Abbreviations

Å	angstrom
Ac	acetyl
Ar	aromatic (generic)
atm	atmosphere(s)
aq	aqueous
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
c	concentration (g/100 mL)
° C	degrees celsius
calcd	calculated
CSA	camphor sulfonic acid
conc.	concentrated
COSY	correlation spectroscopy
Cy	cyclohexyl
d	deutero
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate

DIBAL–H	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
d.r.	diastereomeric ratio
E	entgegen
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
ent	enantiomeric
epi	epimeric
eq	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
h	hour(s)
HBTU	*O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HF•py	hydrogen fluoride-pyridine complex
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry

HSQC	heteronuclear single quantum coherence
Hz	hertz
i or *iso*	iso
IBX	*ortho*-iodoxybenzoic acid
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
2,6-lut.	2,6-lutidine
M	metal
<u>M</u>	molar
m	meta
m	multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
N	normal

n	normal
Nu	nucleophile
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl
OTf	trifluoromethanesulfonate
p	para
Pd/C	palladium on carbon
Ph	phenyl
PhMe	toluene
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
py	pyridine
R	alkyl group (generic)
R	rectus (Cahn–Ingold–Prelog system)
rac	racemic
Rf	retention factor
Rochelle's salt	sodium/potassium tartrate
rt	room temperature
S	sinister (Cahn–Ingold–Prelog system)

s or *sec*	secondary
sat.	saturated
T	temperature
t	triplet
t or *tert*	tertiary
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl
T_r	retention time
TS	transition state
Ts	4-methylbenzenesulfonyl
wt%	weight percent
WSC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
Z	zusammen
δ	chemical shift (parts per million)

Chapter 1

(−)-Nakadomarin A and the Manzamine Alkaloids

I. Isolation and Biological Activity

Since the isolation of manzamine A[1] in 1986, the manzamine family of alkaloids have been enriched continuously by the discovery of new compounds with unprecedented molecular architectures. Members of the family include simple macrocyclic 3-alkylpyridinium salts, such as cyclostellettamine A (**1**), and highly elaborated and complex structures, such as manzamine A (**5**) and sarain A (**7**) (Figure 1.1).[2]

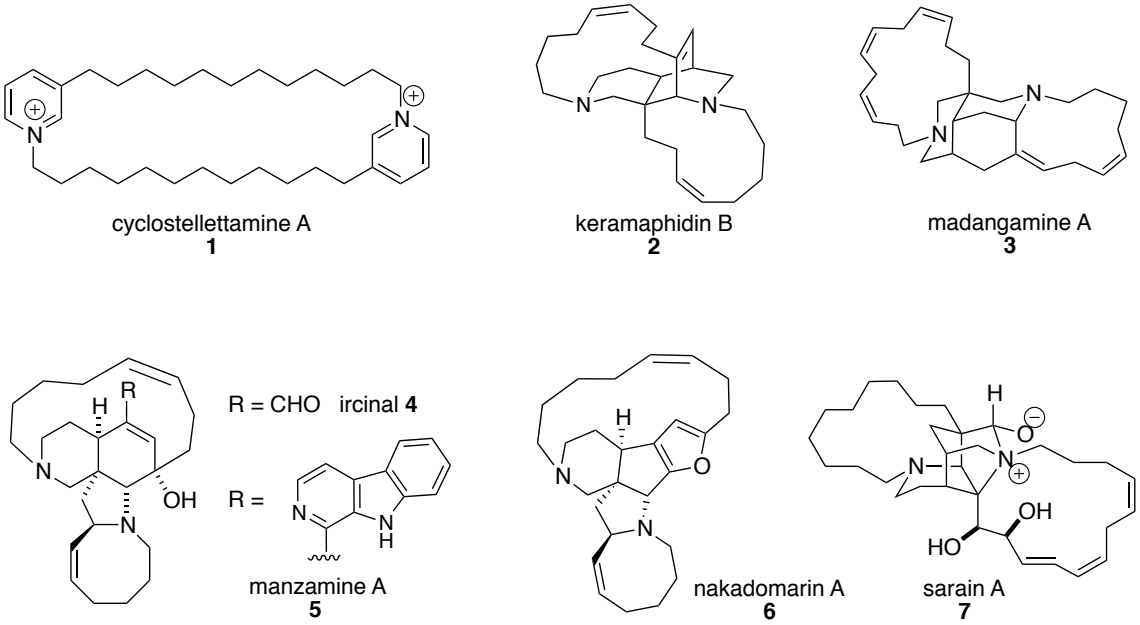


Figure 1.1. Selected alkaloids from the manzamine family.

[1] Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986***, 108,* 6404–6405.

[2] Duval, R.; Poupon, E. in *Biomimetic Organic Synthesis,* Poupon E.; Nay, B. (eds.), Chapter 6, Wiley-VCH, **2011.**

Kobayashi and coworkers reported the isolation of (–)-nakadomarin A (**6**) from an Okinawan marine sponge *Amphimedon sp.* in 1997.[3] Its novel structure constituting an 8/5/5/5/15/6 ring system was elucidated by extensive spectroscopic analysis. The relative stereochemistry was deduced from the NOE correlation data and ^{1}H NMR coupling constants. The first total synthesis of nakadomarin A[4] gave the absolute configuration.

(–)-Nakadomarin A (**6**) has already been shown exhibits a range of therapeutic activities, such as anticancer (murine lymphoma L1210 cells IC_{50} = 1.3 μg/mL, CDK4 IC_{50} = 9.9 mg/mL), antifungal (against *Trichophyton mentagrophytes*, MIC 23 μg/mL), and antibacterial (against *Corynebacterium xerosis*, MIC 11 μg/mL). No further investigation on the biological activity has been reported since its isolation.

II. Biosynthesis

Although the exact biosynthetic path to the manzamine alkaloids was unclear,[1] Baldwin devised a biosynthetic proposal of the manzamine alkaloids (Scheme 1.1).[5] A transannular Diels-Alder reaction of 3-alkylpyridinium derivative **8** would generate polycyclic compound **9**, subsequent reduction of **9** would afford natural product keramaphidin B **2**.[6] Redox reaction of **2** or **9** would afford iminium species **10** and further hydrolysis will lead to aminoaldehyde **11**. A transannular allylic amination is reasoned to

---

[3] Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236–9239.

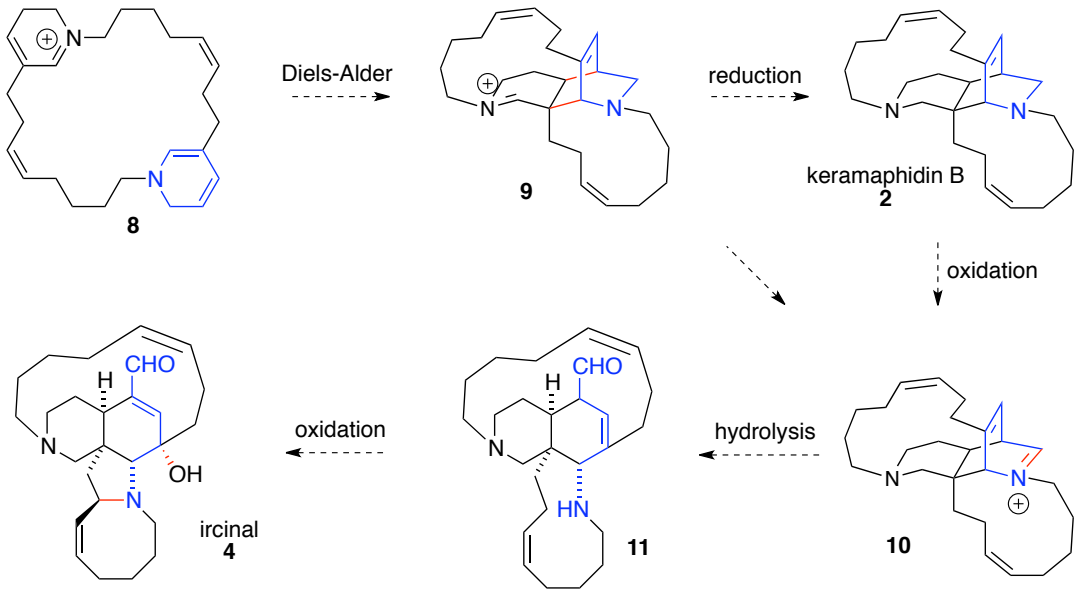
[4] Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484–7485.

[5] (a) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron. Lett*. **1992**, *33*, 2059. (b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661. (c) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154.

[6] (a) Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron Lett.* **1996**, *52*, 2319 and references cited therein. (b) Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51*, 2895.

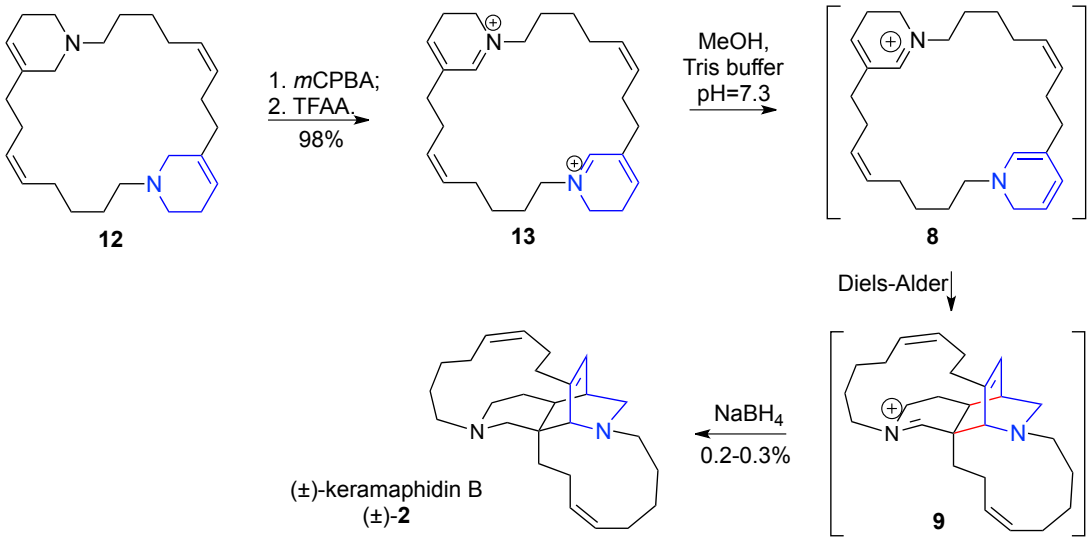
complete the polycyclic skeleton of manzamine alkaloid to generate the natural product ircinal **4**.

Scheme 1.1. Proposed biosynthesis of manzamine alkaloids by Baldwin.



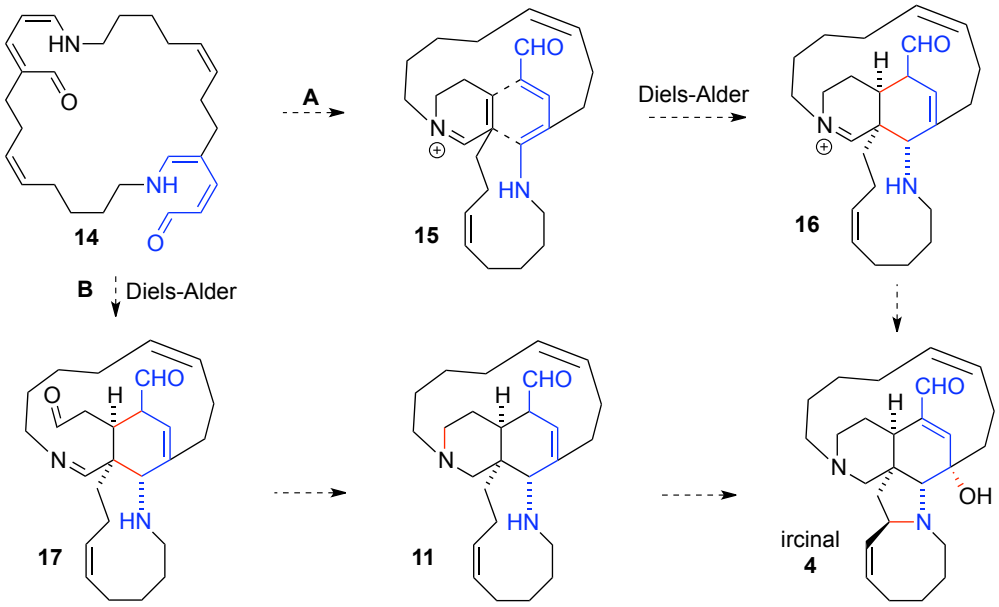
To verify the feasibility of his proposed biosynthesis, Baldwin reported a biomimetic synthesis of keramaphidin B **2** (Scheme 1.2).[5] Oxidation of bisamine **12** with *m*CPBA, followed by treatment with trifluoroacetic anhydride generated diiminium **13**. Tautomerization of **13** under buffered neutral conditions gave **8**, which underwent an intramolecular Diels-Alder reaction to give iminium **9**. Reduction of **9** with $NaBH_4$ gave natural product keramaphidin B **2** in low yield. The major product (60-85%) was the recyclable bis-tetrahydropyridine **12**.

Scheme 1.2. Biomimetic synthesis of keramaphidin B **2.**



Marazano later modified Baldwin's biosynthesis proposal as illustrated in Scheme 1.3.[7] He argued that Zincke aldehdye **14** could undergo a Diels-Alder reaction (path A or B) to give **11** or **16**. Subsequent oxidation would generate natural product ircinal **4**.

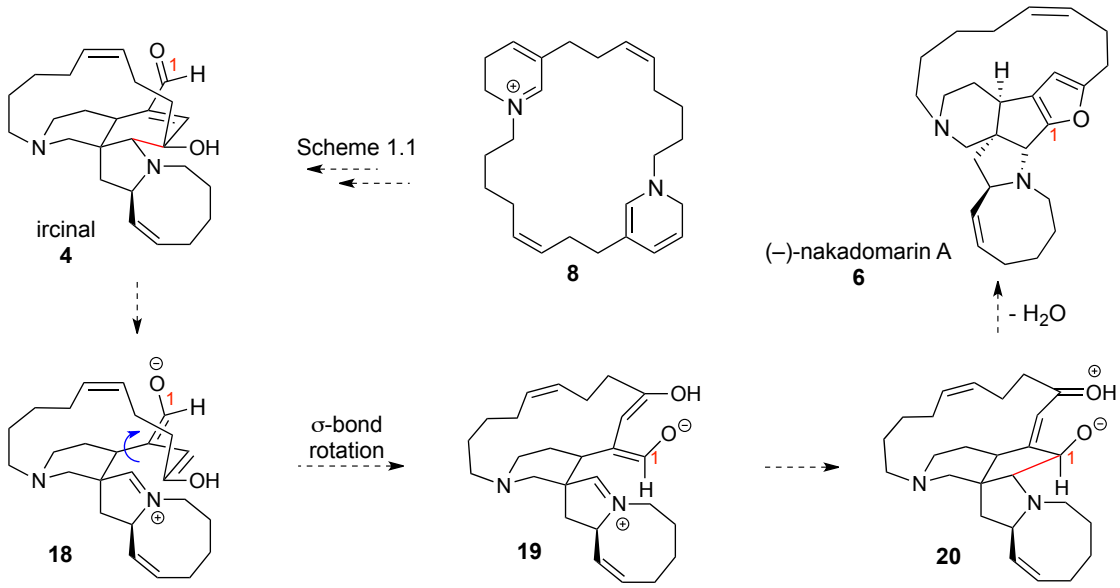
Scheme 1.3. Modified biosynthetic proposal by Marazano.



[7] (a) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. *J. Am. Chem. Soc.* **1998**, *120*, 8026-8034; (b) Wypych, J.; Nguyen, T.; Nuhant, P.; Benechie, M.; Marazano C. *Angew. Chem. Int. Ed.* **2008**, *47*, 5418 –5421.

Kobayashi put forth a biosynthetic proposal for (−)-nakadomarin A **6** from ircinal A **4** (Scheme 1.4).[8] A retro-Mannich reaction of **4** could generate iminium **18**. σ-Bond rotation and a subsequent vinylogous Mannich reaction would give **20**. A final cyclodehydration reaction would generate (−)-nakadomarin A **6**.

Scheme 1.4. Proposed biosynthesis of (−)-nakadomarin A **6**.



III. Previous Total Syntheses of (−)-Nakadomarin A

The unique and complex structure of (−)-nakadomarin presents a great challenge to the synthetic organic chemists. New synthetic methodologies and strategies had been developed for its total synthesis. To date, six groups have reported their total syntheses of (−)-nakadomarin A and/or its enantiomer (+)-nakadomarin A.

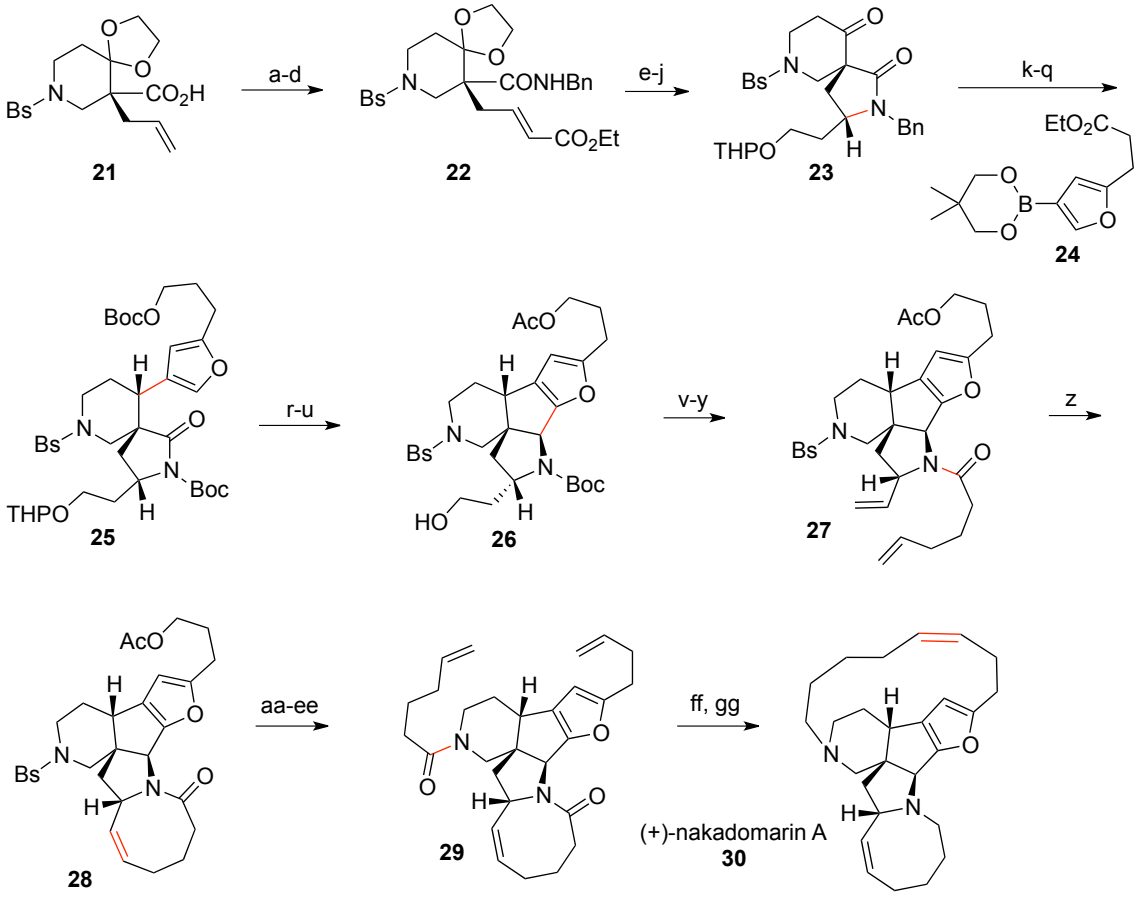
1. The Nishida Synthesis (I)

Nishida and co-workers reported the first total synthesis of (+)-nakadomarin A **30** in 2003 (Scheme 1.5).[4] The synthesis commenced from chiral carboxylic acid **21**, which

[8] Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure. Appl. Chem.* **1999**, *71*, 1123–1126.

was obtained in optically pure form by resolution with cinchonine. Acid **21** was transformed into the unsaturated ester **22** and an intramolecular conjugate addition afforded the bicyclic lactam **23** in modest diastereoselectivity. A Suzuki coupling with **24** incorporated the furan moiety into the molecule, and a followed hydrogenation reaction

Scheme 1.5. Nishida's total synthesis of (+)-nakadomarin A.



Reagents and conditions: (a) $BnNH_2$, WSC•HCl, HOBt, 91%; (b) cat. OsO_4, NMO; (c) $NaIO_4$; (d) Ph_3PCHCO_2Et; (e) DBU, EtOH; (f) 2 N NaOH; (g) AcCl, EtOH, 54% (8 steps); (h) $LiBH_4$, 99%; (i) 70% $HClO_4$, 91%; (j) DHP, cat. CSA, 91%; (k) i) $LiN(TMS)_2$, THF, -78°C, ii) $PhNTf_2$, 87%; (l) **24**, $PdCl_2(dppf)$, K_3PO_4, 80°C, 95%; (m) i) H_2, 10% Pd-C, 71%, ii) PPTS, EtOH, iii) separation of diastereomers, (iv) DHP, cat. CSA, 69%; (n) $LiBH_4$, 99%; (o) Li, liq. NH_3; (p) $PhSO_2Cl$, aq $NaHCO_3$, 80% (2 steps); (q) $(Boc)_2O$, Et_3N, cat. DMAP, 98%; (r) DIBAL-H; (s) Ac_2O, pyridine, 80% (2 steps); (t) p-TsOH; (u) 1 N HCl, 87% (2 steps); (v) 2-nitrophenylselenocyanate, *n*-Bu_3P; (w) *m*CPBA, aq K_2HPO_4; (x) TFA; (y) 5-hexenoic acid, WSC•HCl, HOBt, 73% (4 steps); (z) Grubbs 2nd generation catalyst (20 mol %), 2 mM, 50 °C, 1.5 h; (aa) 2 N NaOH, 64% (2 steps); (bb) Dess-Martin periodinane, 80%; (cc) Ph_3PCH_2, 72%; (dd) Na, naphthalene; (ee) 5-hexenoic acid, WSC·HCl, HOBt, 77% (2 steps); (ff) Grubbs 1st generation catalyst (15 mol %), 0.5 mM, 26%(*Z*), 44%(*E*); (gg) Red-Al, 86%.

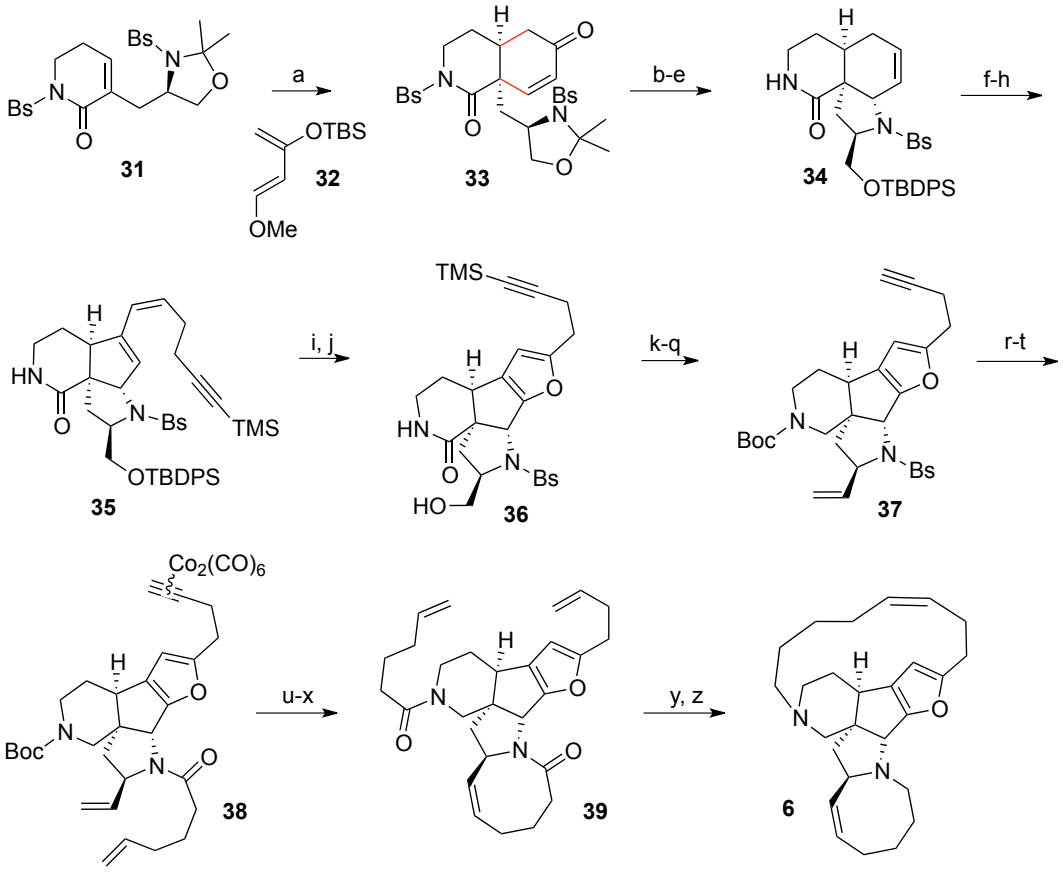
gave **25**. An intramolecular cyclization of furan with the iminium generated the tetracyclic compound **26**. The macrocycle and the azocine ring were both formed with ring closing olefin methathesis reaction. A mixture of *Z/E* olefins was obtained in the macrocyclic RCM reaction of **29** and fortunately the two isomers could be separated from each other. A final amide reduction generated **30**. The NMR spectra of **30** matched with those of the natural product, but a careful comparison of the specific rotation showed that it was the enantiomer. The total synthesis of **30** was completed in 38 steps with the longest linear sequence, and it proved the structure and absolute configuration of the natural product.

2. The Nishida Synthesis (II)

Following their first total synthesis of (+)-nakadomarin A **30**, the Nishida group reported the first total synthesis of natural enantiomer (–)-nakadomarin A **6** in 2004.[9] Starting from unsaturated amide **31**, which was obtained from L-serine in 10 steps, a Diels-Alder reaction with Danishefsky diene **32** afforded bicyclic compound **33** with poor diastereoselectivity. Cycloaddition of diene **35** with singlet O_2, followed by base and acid mediated rearrangement formed the furan ring of tetracyclic compound **36**. As in the previous synthesis of **30**, the remaining macrocycle and azocine rings were both formed by ring closing metathesis reactions. Separation of the macrocyclic olefin isomers and amide reduction completed natural product (–)-nakadomarin A **6** (Scheme 1.6).

[9] Ono. K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020–2023.

Scheme 1.6. Nishida's total synthesis of (–)-nakadomarin A.



Reagents and conditions: (a) **32** (3.0 equiv), neat, 180 °C, 1 h; then TFA, 52% (diastereomer 35%); (b) $NaBH_4$, $CeCl_3$•$7H_2O$, 98% (d.r.=2:1); (c) HCl, 70%; (d) TBDPSCl, imidazole; (e) Na/anthracene, 74% (two steps); (f) O_3; then Me_2S; (g) *N*-methylanilinium trifluoroacetate, 75% (two steps); (h) $IPh_3PCH_2CH_2CH_2CCTMS$, 76%; (i) O_2, halogen lamp, Rose Bengal, quant.; (j) t-BuOK; then HCl; (k) Dess-Martin periodinane, 90%; (l) $TMSCH_2MgCl$, 83%; (m) BF_3•Et_2O; (n) K_2CO_3, MeOH, 81% (two steps); (o) Boc_2O, DMAP, Et_3N, 93%; (p) DIBAL-H; (q) Et_3SiH, BF_3•Et_2O, 84% (two steps); (r) Na/naphthalene; (s) 5-hexenoyl chloride, Et_3N, 92% (two steps); (t) $Co_2(CO)_8$, 91%; (u) Grubbs 2nd generation catalyst (25 mol%), 83%; (v) *n*-Bu_3SnH, 75%; (w) TFA; (x) 5-hexenoyl chloride, Et_3N, 92% (two steps); (y) Grubbs 1st generation catalyst (20 mol%), 26% (*Z*) + 46% (*E*); (z) Red-Al, 92%. Bs = benzenesulfonyl.

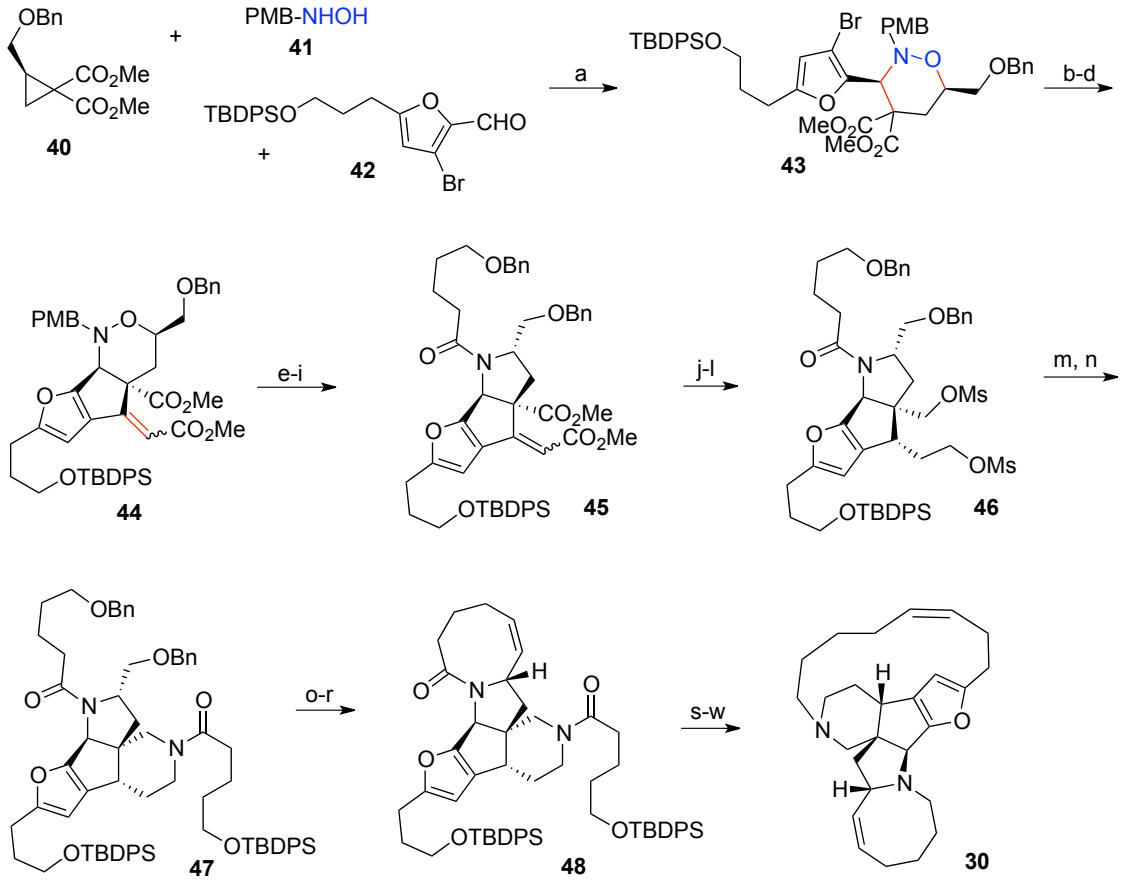
3. The Kerr Synthesis

The Kerr group reported a total synthesis of (+)-nakadomarin A **30** in 2007,[10] (Scheme 1.7). The synthesis featured a three-component dipolar cycloaddition reaction

[10] Young, I.; Kerr, M. *J. Am. Chem. Soc.*, **2007**, *129*, 1465–1469.

developed by their group.[11] Cyclopropane malonate **40**, hydroxylamine **41** and aldehyde **42** underwent a $Yb(OTf)_3$ catalyzed three-component reaction to afford product **43** in good yield. An intramolecular Heck reaction generated tricyclic compound **44**. Reductive cleavage of the weak N-O bond of **44** and an intramolecular S_N2 alkylation formed the

Scheme 1.7. Kerr's Total synthesis of (+)-nakadomarin A.



Reagents and conditions: (a) 15 mol% $Yb(OTf)_3$, 87%; (b) DIBAL-H, 87%; (c) $(MeO)_2P(O)CH_2CO_2Me$, t-BuOK, 93%; (d) $Pd(PPh_3)_4$, Ag_2SO_4, NEt_3, 82%; (e) DDQ, 56% after 1 recycle; (f) $ClC(O)(CH_2)_4OBn$, NEt_3, 89%; (g) 0.1 M SmI_2 (5:1 ratio of double bond isomers); (h) MsCl, NEt_3, DMAP; (i) t-BuOK, 65% (three steps); (j) $NiCl_2•6H_2O$, $NaBH_4$, Na_2CO_3, 67% (14:1 diastereomers); (k) $LiAlH_4$; (l) MsCl, NEt_3, DMAP, 79% (two steps), 14:1 diastereomers; (m) NH_3; (n) $ClC(O)(CH_2)_4OTBDPS$, NEt_3, 77% (two steps); (o) BCl_3, 71%; (p) IBX, DMSO; (q) t-BuOK, $MePPh_3Br$, 30-45% (two steps); (r) 20 mol % Grubbs 2nd generation catalyst, 84%; (s) MeOH, AcCl; (t) Dess-Martin periodinane, 70% (two steps); (u) t-BuOK, $MePPh_3Br$; (v) 30 mol % Grubbs first generation catalyst, 28% *E*-isomer (two steps), yield for *Z*-isomer given after reduction; (w) Red-Al, 20% (three steps).

[11] (a) Young, I.; Kerr, M. *Angew. Chem. Int. Ed*. **2003**, *42*, 3023-3026; (b) Young, I.; Kerr, M. *Org. Lett.* **2004**, *6*, 139-141. (c) Young, I.; Williams, J.; Kerr, M. *Org. Lett*. **2005**, *7*, 953-955.

pyrrolidine ring of compound **45**. Double alkylation of **46** formed the piperidine ring of the tetracyclic compound **47**. RCM reaction generated both the macrocyclic and azocine rings. Separation of the macrocyclic olefin isomers, followed by amide reduction gave (+)-nakadomarin A **30**.

4. The Dixon Synthesis

The Dixon group reported a convergent total synthesis of (−)-nakadomarin A **6** in 2009 (Scheme 1.8).[12] The malonate Fragment **51** was prepared from the D-pyroglutamic acid derivative **49** in 6 steps and the nitro olefin fragment **54** was prepared in 4 steps from the phosphate **52**. A Michael reaction of malonate **51** with nitro olefin **54** catalyzed by a cinchona-derived organocatalyst **55** afforded product **56**, which underwent a three-component reaction [13] with 5-hexenyl-1-amine and formalin to afford tetracyclic compound **57**. Functional group manipulation and an acid mediated cyclization reaction of the pedant furan with iminium afforded pentacyclic compound **58**. Macrocyclization via RCM, followed by separation of the olefin isomers by HPLC, generated natural product (−)-nakadomarin A **6**. A later improvement with the *Z* selective RCM reaction afforded the natural product in higher selectivity.[14] Two additional total syntheses of **6** with the same fragment coupling strategy were reported from the same group.[15]

---

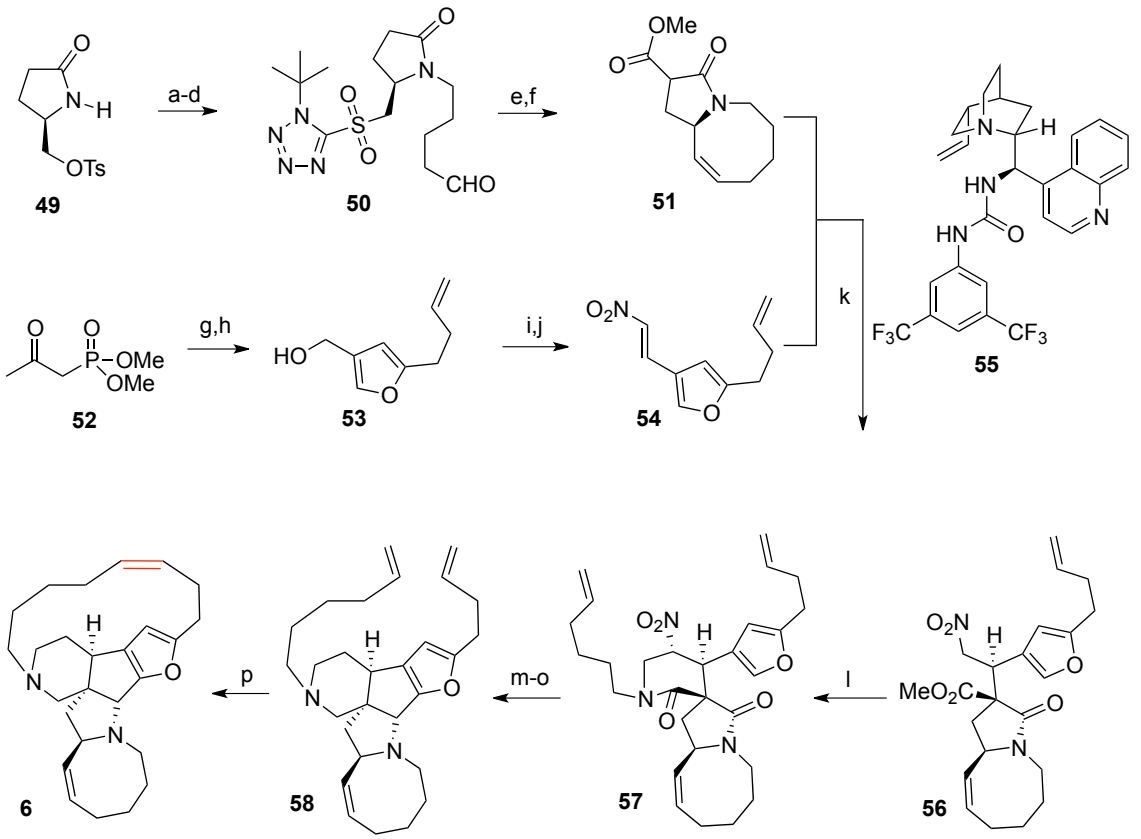
[12] Jakubec, P.; Cockfield, D.; Dixon, D. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

[13] Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.*, **2008**, *10*, 4267–4270.

[14] (a) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88−93. (b) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726-2740.

[15] (a) Kyle, A. F.; Jakubec, P.; Cockfield, D. M; Cleator, E.; Skidmore J.; Dixon, D. J. *Chem. Comm.* **2011**, *47,* 10037-10039. (b) Jakubec, P.; Kyle, A.F; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52,* 6094-6097.

Scheme 1.8. Dixon's total synthesis of (−)-nakadomarin A.



Reagents and conditions: (a) 1-*tert*-butyl-1*H*-tetrazole-5-thiol, NaH, 96%; (b) 2-(4-bromobutyl)-1,3-dioxolane, NaH, Bu_4NI (cat.), 71%; (c) *m*-CPBA, 78%; (d) HCl, 98%; (e) Cs_2CO_3, 56%; (f) LHMDS, dimethylcarbonate, 82%. (g) NaH, BuLi, allylbromide, then 2-oxopropane-1,3-diyl diacetate, 42%; (h) HCl, 69%; (i) $(COCl)_2$, DMSO, Et_3N, 86%; (j) $MeNO_2$, KOH, then MsCl, Et_3N, 88%. (k) organocatalyst **55** (15 mol %), toluene, 30 °C, 8 days, 57%, 91:9 *dr*; (l) hex-5-enamine, $(CH_2O)_n$, 68%; (m) AIBN, Bu_3SnH, 70%; (n) $LiAlH_4$, then HCO_2H, 86%; (o) DIBAL-H, then HCl, 41%; (p) Grubbs first-generation catalyst, (+)-CSA, 62%, 63:37 *Z*/*E*.

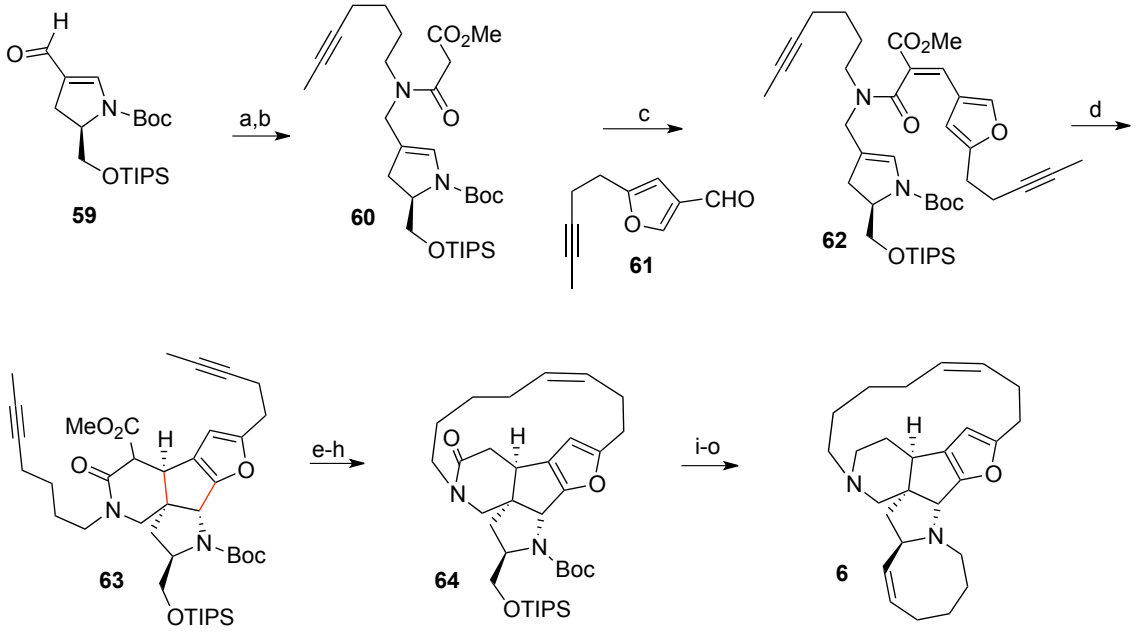
5. The Funk Synthesis

The Funk group reported a total synthesis of (−)-nakadomarin A **6** in 2010 (Scheme 1.9).[16] Compound **60** was obtained from the *D*-pyroglutamic acid derivative **59**, and underwent a Knoevenagel condensation with aldehyde **61** to give compound **62**. A Lewis acid $InCl_3$ catalyzed Michael addition/Pictet-Spengler cyclization reaction sequence[17]

[16] Nilson, M. G.; Funk, R. L. *Org. Lett.*, **2010**, *12*, 4912-4915.
[17] Nilson, M. G.; Funk, R. L. *Org. Lett.*, **2006**, *8*, 3833–3836.

produced tetracyclic compound **63**. Ring closing alkyne metathesis of **63** followed by Lindlar reduction formed macrocycle **64**. Generation of the azocine ring by RCM and amide reduction finished the natural product **6**.

Scheme 1.9. Funk's total synthesis of (–)-nakadomarin A.



Reagents and conditions: (a) 5-heptynylamine, $NaBH_4$; (b) methyl malonyl chloride, 66%, 2 steps; (c) PhCOOH, piperidine, 87%; (d) $InCl_3$ (10 mol%), 79%; (e) KOH; H_3O^+; (f) PhMe, heat, 80%, 2 steps; (g) $(t\text{-}BuO)_3WC\text{-}t\text{-}Bu$ (25 mol%), 77%; (h) H_2, Lindlar catalyst. (i) TBAF, 80%, 2 steps; (j) IBX, DMSO; (k) $Cp_2TiCH_2AlClMe_2$, 68%, 2 steps; (l) TFA; (m) 5-hexenoyl chloride, Et_3N, 74%, 2 steps; (n) Grubbs first generation catalyst; (o) $AlCl_3$, $LiAlH_4$, 58%, 2 steps.

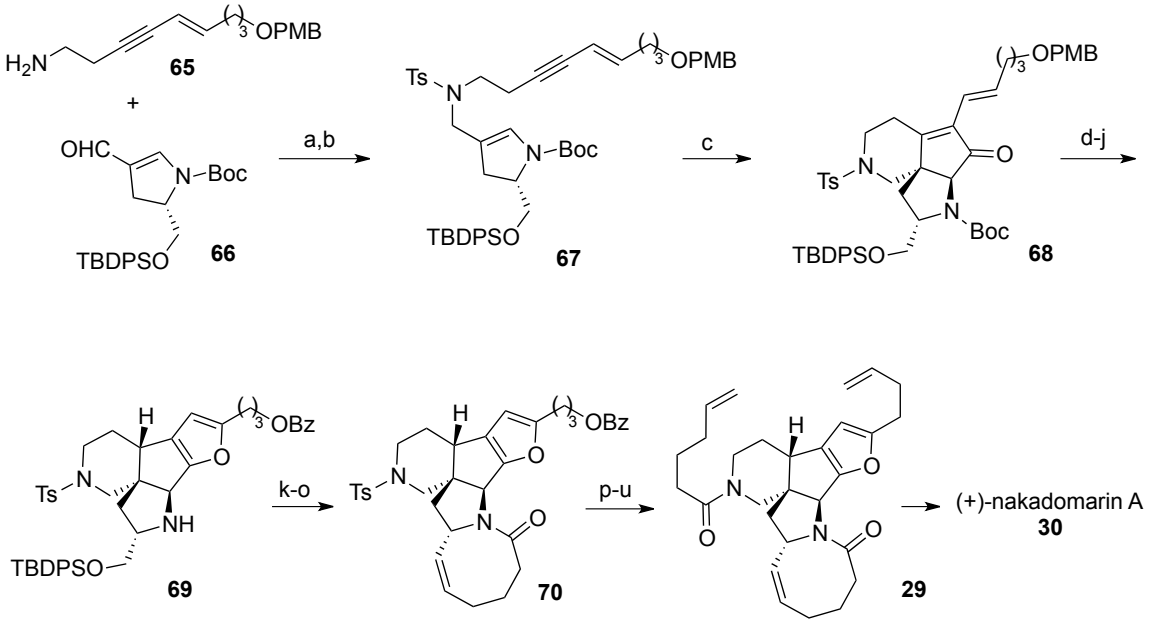
6. The Mukai Formal Synthesis

The Mukai group reported a formal total synthesis of (+)-nakadomarin A **30** in 2010 (Scheme 1.10).[18] Reductive amination of amine **65** with the *D*-pyroglutamic acid derived aldehyde **66** afforded enyne **67**, which underwent a Pauson-Khand cyclization to give tricyclic compound **68**. Furan formation and hydrogenation generated tetracyclic compound **69**. RCM reaction generated the azocine ring, which established the

[18] Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800-1803.

pentacyclic framework of compound **70**. **70** was transformed into the diene **29**, a intermediate in Nishida and Kerr's total synthesis of (+)-nakadomarin A, which completed a formal synthesis of (+)-nakadomarin A.

Scheme 1.10. Mukai's formal synthesis of (+)-nakadomarin A.



Reagents and conditions: (a) $MgSO_4$, MeOH, then $NaBH_4$; (b) TsCl, pyridine, 69%; (c) $Co_2(CO)_8$; then *n*-BuSMe, 60%. (d) DDQ; (e) BzCl, pyridine, 90%; (f) OsO_4 (4 mol%), NMO; (g) CSA, 80%; (h) FmocCl, $NaHCO_3$, 90%; (i) 10 mol% Pd/C, H_2, 51%; (j) piperidine, quant.; (k) 5-hexenoyl chloride, Et_3N; (l) TBAF, 55%; (m) Dess-Martin periodinane; (n) $CH_2{=}PPh_3$; (o) Grubbs 2nd generation catalyst, 84%; (p) NaOH; (q) IBX; (r) $CH_3C(N_2)PO(OMe)_2$, K_2CO_3, 73%; (s) Na, naphthalene; (t) 5-hexenoic acid, EDC•HCl, HOBT, 69%; (u) Lindlar catalyst, H_2, 83%.

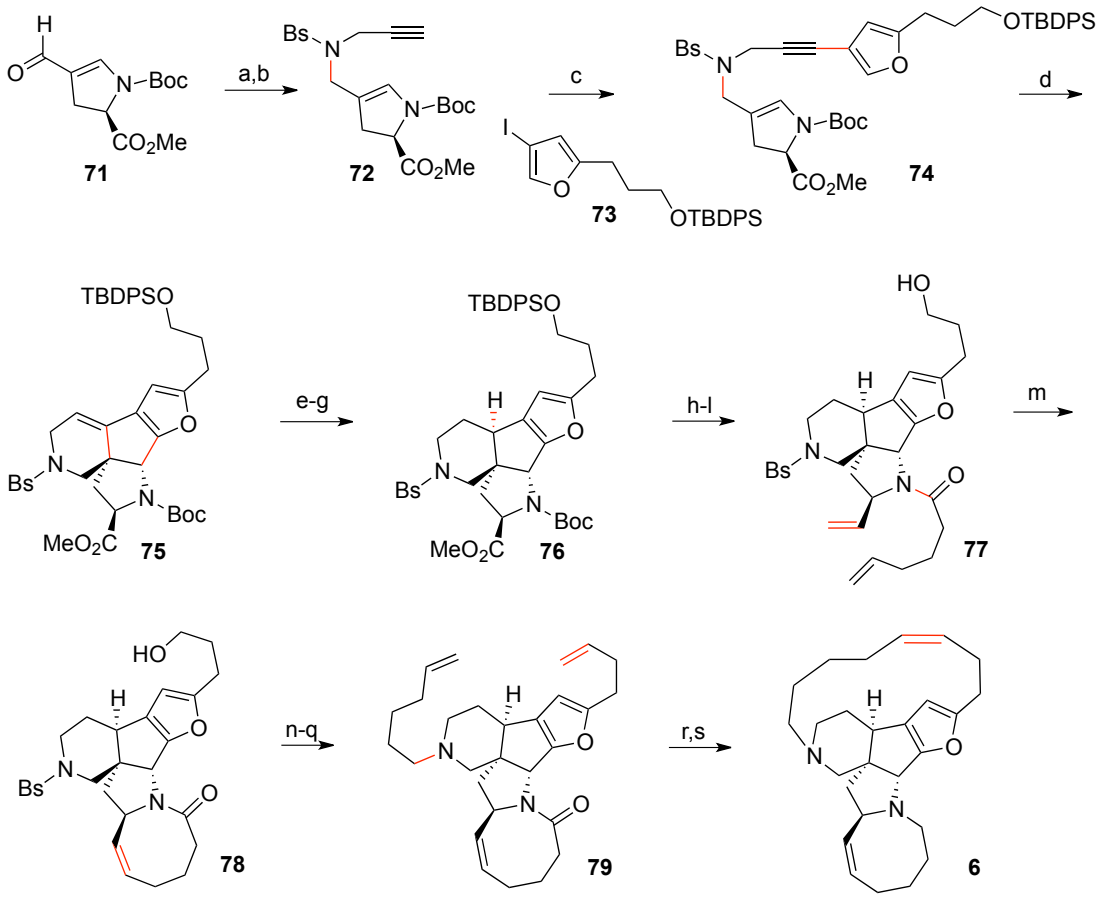
7. The Zhai Synthesis

The most recent total synthesis of (–)-nakadomarin A **6** came from the Zhai group in 2011 (Scheme 1.11).[19] Alkyne **72** was obtained from *D*-pyroglutamic acid derivative **71**, and coupled with iodide **73** to give enyne **74**. A $PtCl_2$ catalyzed cascade reaction sequence [20] of **74** afforded tetracyclic compound **75**. Olefin hydroboration and

[19] Cheng, B.; Wu, F.; Yang, X.; Zhou, Y.; Wan, X.; Zhai H. *Chem. Eur. J.* **2011**, *17*, 12569-12572.
[20] (a) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.*, **2008**, *10*, 1791–1793. (b) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367.

deoxygenation gave the tetracyclic core structure of (–)-nakadomarin A **76**. Ring closing metathesis of diene **77** and **79** generated the azocine ring and the macrocycle. HPLC separation of two olefin isomers, followed by amide reduction gave natural product **6**.

Scheme 1.11. Zhai's total synthesis of (–)-nakadomarin A.



Reagents and conditions: a) propargylamine•HCl, TEA, $NaBH_4$, MeOH; b) BsCl, TEA, 54% (2 steps); c) **73**, $[Pd(PPh_3)_2Cl_2]$, CuI, TEA, 87%; d) $PtCl_2$, 81%; e) BH_3•SMe_2, H_2O_2, NaOH, 81%; f) NaH, CS_2, MeI; g) Bu_3SnH, AIBN, 94% (2 steps); h) DIBAL-H; i) $MePPh_3Br$, tBuOK, 74% (2 steps); j) $ZnBr_2$; k) 5-hexenoyl chloride, TEA, DMAP; l) TBAF, 70% (3 steps); m) Grubbs second-generation catalyst (20 mol%); n) Swern oxidation; o) $MePPh_3Br$, K_2CO_3, 18-crown-6, 70% (3 steps); p) Na, naphthalene; q) 6-bromo-1-hexene, K_2CO_3, 91% (2 steps); r) Grubbs first-generation catalyst (25 mol%), CSA, *Z/E* about 2:1, 31%; s) Red-Al, 85%.

IV. A Macrocyclic Approach to Polycyclic Structures

It has been a long theme of research in the Evans group to synthesize polycyclic natural products from acyclic precursors,[21] in concomitant with efficient synthetic methodology development for acyclic stereochemical control.[22]

A biomimetic total synthesis of polycyclic natural product (–)-FR182877 was reported in 2002 from Evans lab (Scheme 1.12).[21b,21c] Two acyclic chiral compounds (**80** and **81**), obtained from two (4*R*)-4-benzyl-2-oxazolidinone-mediated boron aldol reactions,[23] were transformed into the boronic acid (**82**) and vinyl bromide (**83**) respectively. A Suzuki coupling reaction united the two fragments and an intramolecular malonate allylation reaction[24] generated the macrocycle. The key double transannular Diels-Alder reaction of macrocycle **84** generated pentacyclic product **86**. Conformational analysis of the macrocycle revealed that an *endo* transition state dictated the first diastereoselective Diels-Alder reaction which gave intermediate **85**, followed by a rapid hetero-Diels-Alder reaction to the resultant pentacycle **86**, which was further elaborated to the natural product (–)-FR182877 (**87**).

---

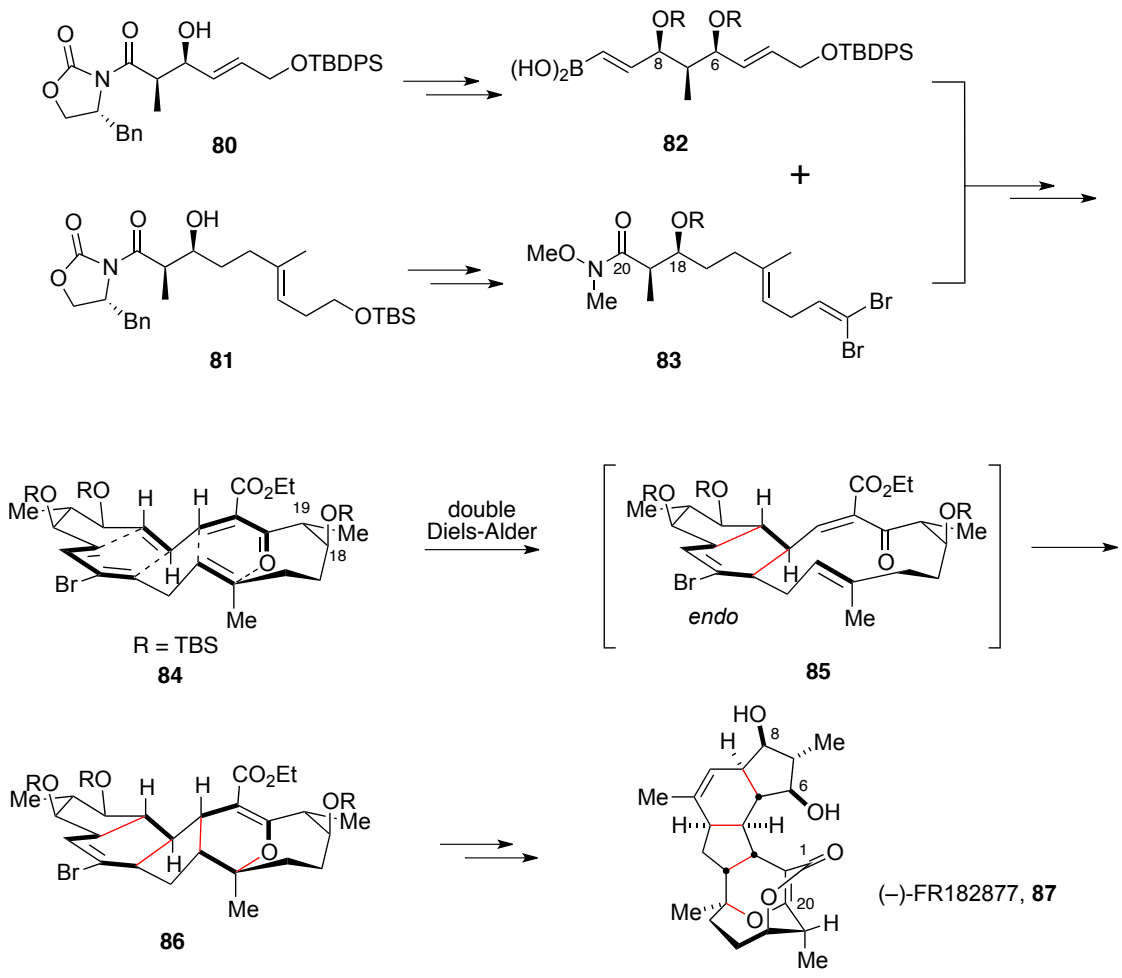
[21] (a) (+)-Miyakolide: Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816. (b) (−)-FR182877: Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787-1790. (c) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (d) (+)-Clavolonine: Evans, D. A.; Scheerer, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 6038-6042. (e) Salvinorin A: Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007,** *129*, 8968. (f) Tetracycline intermediate: Wzorek, J. S.; Knöpfel, T. F.; Sapountzis, I.; Evans, D. A. *Org. Lett.*, **2012**, *14*, 5840–5843. (g) Phorbol intermediate: Catino, A. J.; Sherlock, A.; Shieh, P.; Wzorek, J. S.; Evans, D. A. *Org. Lett.*, **2013**, *15*, 3330–3333.

[22] For examples of synthetic methodologies, see: (a) aldol reaction: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.*, **1981**, *103*, 3099-3111. (b) BOX-ligand based reaction: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.*, **2000**, *33*, 325–335.

[23] Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77; Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

[24] Phoenix, S.; Bourque, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 4149.

Scheme 1.12. Total synthesis of (–)-FR182877.

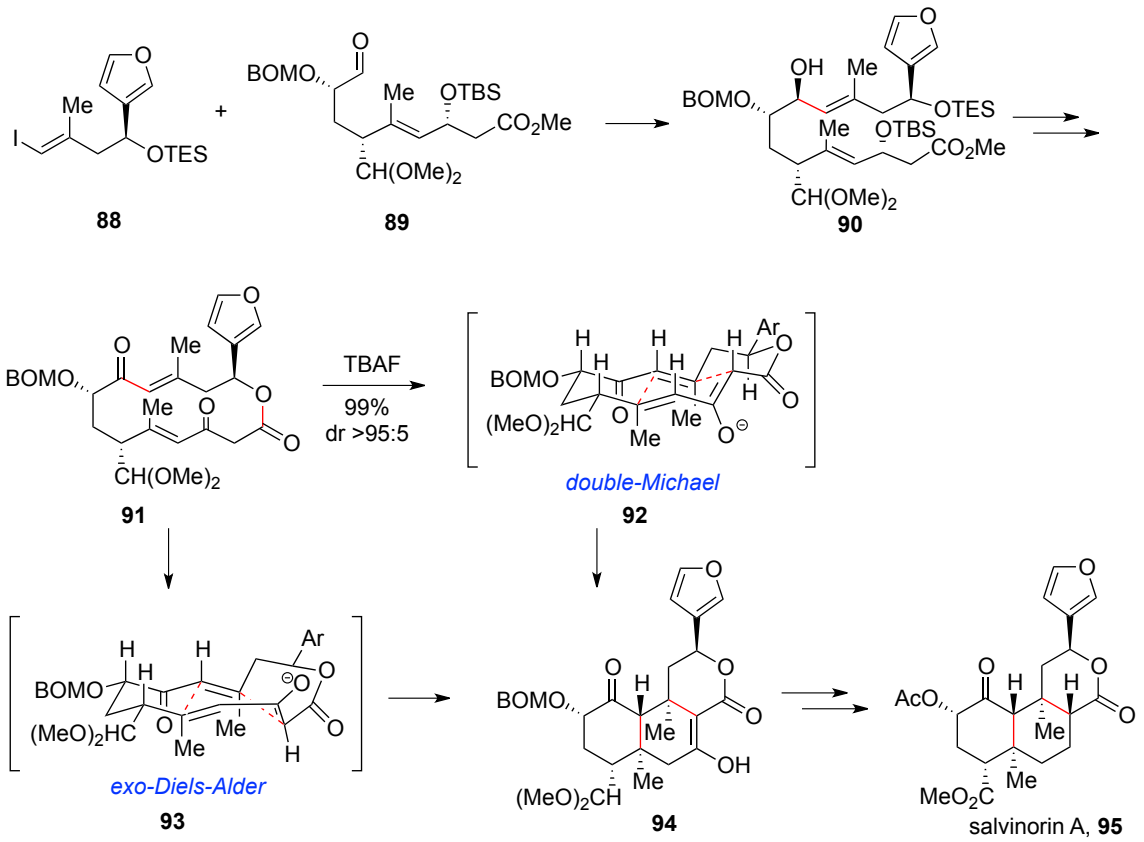


A more recent illustration of the macrocyclic approach came from the total synthesis of salvinorin A, a potent and selective κ opioid receptor agonist (Scheme 1.13).[5e] The chiral vinyl iodide fragment **88**, which was prepared from the CBS reduction,[25] was transformed into the vinyl magnesium bromide, and coupled with aldehyde **89** to give **90**. The three chiral centers of **89** were prepared from a Ni(II)-(*R*)-BINAP catalyzed

[25] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986-2012 and references therein.

orthoester alkylation of thiazolidinethione,[26] a selective aldol addition of acetate-derived chiral auxiliary,[27] and an (-)-*N*-methylephedrine-mediated zinc acetylide addition reaction.[28]

Scheme 1.13. Total synthesis of salvinorin A.



Macrolactonization of the seco-acid generated the macrocycle.[29] The key transannular cyclization of macrocycle **91** mediated by TBAF gave product **94** in good yield and diastereoselectivity. A double Michael addition via **92** was proposed for this process;

[26] Evans, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2005**, *128*, 10506-10507.

[27] Nagao, Y.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.

[28] Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.

[29] (a) Shiina, I.; Kubota, M.; Ibuka, R.; T*etrahedron Lett.* **2002**, *43*, 7535-7539. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822-1830.

however, an *exo*-Diels-Alder reaction via **93** was also possible. From the cyclization product **94**, salvinorin A (**95**) was obtained in a few steps.

From the analysis of the two total syntheses presented above, the overall sequence of this macrocyclic synthetic strategy can be summarized into the following four general steps: (1) Building the acyclic precursors with appropriate stereochemistry. (2) Generating the macrocycle. (3) Transforming the macrocycle to the polycyclic skeleton. (4) Further functional group manipulation to the final target. The success of this strategy would rely on the well-established acyclic stereochemical control,[30] efficient macrocyclization methods,[31] and powerful conformational analysis.[32,33]

To further extend the scope of this strategy, the Evans group initiated a program directed toward the total synthesis of polycyclic manzamine alkaloids, including (–)-nakadomarin A[34] and manzamine A.[35]

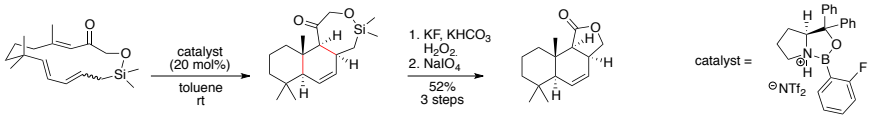
---

[30] *(a) Comprehensive Asymmetric Catalysis, I-III.* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. (eds.), Springer, **1999**. (b) *Asymmetric Synthesis-the Essentials*. Christmann, M.; Bräse, S. (eds), Wiley-VCH, **2007**.

[31] Some reviews on macrocyclization reactions: (a) Roxburgh, C. *Tetrahedron* **1995**, *51*, 9767-9822. (b) Paterson, I.; Norcross, R. D. *Chem. Rev.* **1995**, *95*, 2041-2114. (c) A. Parenty, X. Moreau, Gilles Niel, J.-M. Campagne *Chem. Rev.*, **2013**, *ASAP*; (d) A. Parenty, X. Moreau, J.-M. Campagne *Chem. Rev.*, **2006**, *106*, 911–939. (e) RCM/RCAM: Ana, G.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101. (f) Fukuyama-Mitsunobu reaction: Kan, T., Fukuyama, T. *Chem. Comm.*, **2004**, 353-359. (g) Prins reaction: Crane, E. A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8316–8326.

[32] (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981-3996. (b) Wzorek, J. S. PhD Thesis, Harvard University, **2012**.

[33] The transannular reaction can also be subjected to catalyst-controlled conditions, e.g. the chiral Lewis acid catalyzed transannular Diels-Alder reaction afforded the tricyclic compound in good enantioselectivity. Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736–1740.



[34] Aye, Y. PhD Thesis, Harvard University, **2009**.

[35] (a) Weiss, A. Postdoctoral Report, Harvard University, **2011**; (b) Fodor, M. Postdoctoral Report, Harvard University, **2012**.

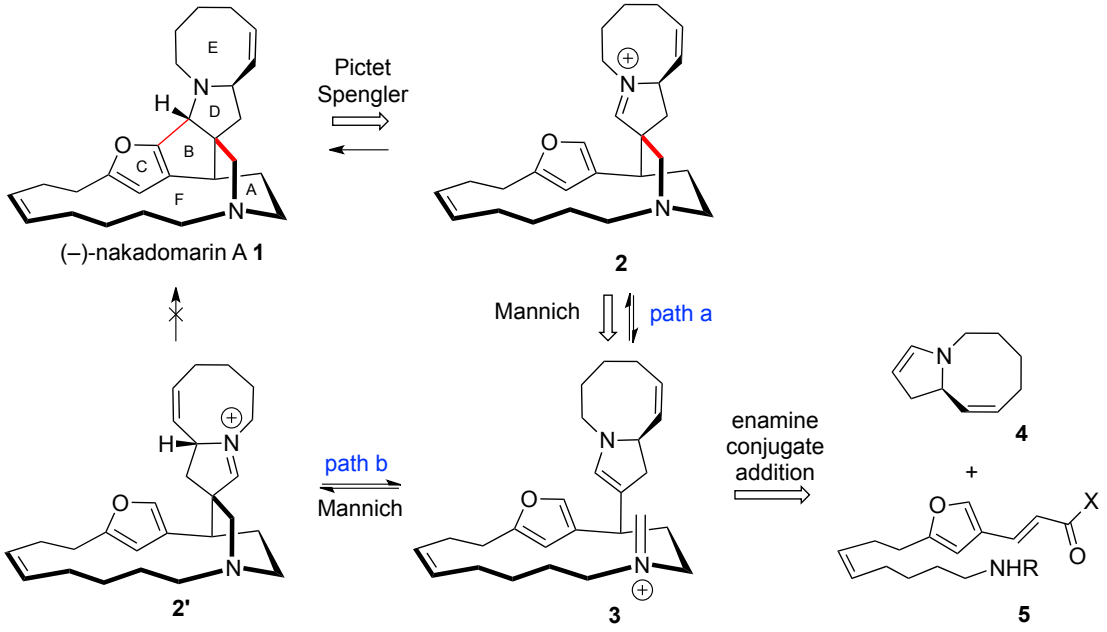
Chapter 2

First Generation Route to the Total Synthesis of (−)-Nakadomarin A

I. Retrosynthetic Analysis

Our first retrosynthetic plan for (–)-nakadomarin A (**1**) features a cascade Mannich/Pictet-Spengler reaction sequence to form rings A and B from macrocyclic intermediate **3** (Scheme 2.1). The assumption behind this strategy is that the Mannich reaction of **3** would be reversible,[1] therefore iminium **2** (path a) could be formed and further cyclized to generate **1**, while the other possible iminium **2'** (path b) could not undergo further cyclization and would regenerate **3**. Compound **3** can be disassembled into two fragments enamine **4** and furan **5**, both of similar size and complexity.

Scheme 2.1. Retrosynthetic analysis of (–)-nakadomarin A.



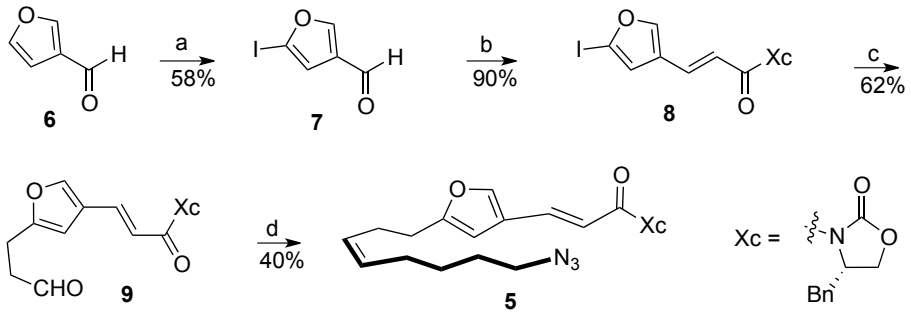
[1] (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. For general reviews on Mannich reaction, see: (b) *Comprehensive Organic Synthesis* (eds. Trost, B. M.; Fleming, I.), Vol. 2, Chapter 4, Pergamon, Oxford, **1991**. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352-359. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045-1070.

II. Results and Discussion

1. Furan Fragment

The furan fragment was prepared from 3-furancarboxaldehyde **6** (Scheme 2.2). Regioselective lithiation[2] of **6** and quenching with iodine gave the iodinated product with 5:1 regioselectivity, favoring the desired product **7**. The two regioisomers was separated by flash column chromatography and the desired iodide **7** was obtained in 50-60% yield on multi-gram scale. Horner-Wadsworth-Emmons olefination[3] of **7** generated the unsaturated imide **8**. Heck cross coupling of **8** with allyl alcohol under Jeffery's condition[4] provided aldehyde **9**, which underwent a Wittig olefination reaction[5] to afford the desired fragment **5**.

Scheme 2.2. Preparation of furan fragment.



Reagents and conditions: (a) morpholine, *n*-BuLi, THF; *s*-BuLi; I_2; 58%; (b) Et_3N, LiCl, $(MeO)_2POCH_2COXc$, THF, 52%, 2 steps; (c) $Pd(OAc)_2$, $NaHCO_3$, $(Bu)_4NBr$, allyl alcohol, DMF, 62%; (d) t-BuONa, $N_3(CH_2)_5PPh_3Br$, THF, 40%.

---

[2] Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126-3131. Initial attempts to trap the organolithium intermediate with homoallylic or homopropargylic halides failed, only elimination products from the alkylhalides (diene and enyne) were obtained.

[3] (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61-63. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738.

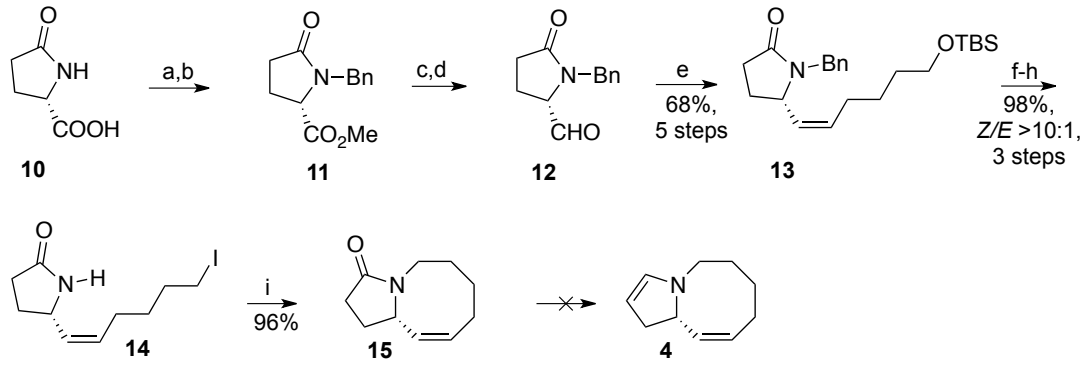
[4] Jeffery, T. *Tetrahedron Lett.* **1991**, 32, 2121.

[5] (a) Wittig, G., Schollkopf, U. *Chem. Ber.* **1954**, *97*, 1318-1330. (b) Wittig, G., Haag, W. *Chem. Ber.* **1955**, *88*, 1654-1666. (c) Chhen, A.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 4953–4956.

2. Enamine Fragment[6]

The enamine fragment was prepared from pyroglutamic acid **10** (Scheme 2.3). Protection of amide and carboxylic acid gave ester **11**, which was then converted to aldehyde **12**. A Wittig olefination afforded cis-olefin **13**. Both benzyl and silyl protecting groups were then removed, and the alcohol was transformed into iodide **14**. An intramolecular *N*-alkylation of **14** formed the azocine ring and afforded bicyclic lactam **15** in high yield. Unfortunately, attempted reduction of lactam **15** to enamine **4** failed, presumably due to the high sensitivity and over-reduction of enamine.

Scheme 2.3. Attepted synthesis of enamine.



Reagents and conditions: (a) $SOCl_2$, MeOH; (b) NaH, BnBr; (c) $LiBH_4$; (d) SO_3•py, DMSO, *i*-Pr_2NEt; (e) NaHMDS, $TBSO(CH_2)_5PPh_3I$. 68%, 5 steps; (f) Li, liq. NH_3; (g) TBAF, AcOH; (h) polymer-PPh_3, I_2, imidazole, 98%, 3 steps; (i) NaH, 96%.

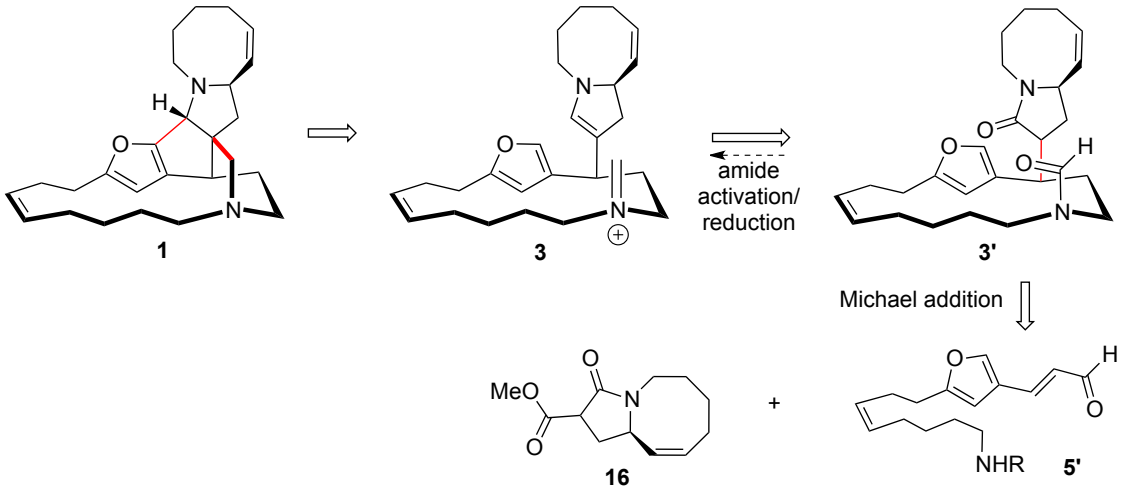
III. Modified First Generation Route

Due to the difficulties in obtaining enamine fragment **4**, bicyclic malonate **16** was chosen as an enamine surrogate, and enal **5′** as the Michael acceptor. Iminium **3** could be generated from semi-reduction or controlled activation of bisamide **3′** (Scheme 2.4).

---

[6] This fragment was investigated by former graduate student Dr. Yimon Aye. A minimum of 85% ee of the bicyclic lactam was estimated by ^1H NMR analysis with chiral shift reagent (+)- and (−)-enantiomers of $Eu(hfc)_3$ (0.6 equiv) in $CDCl_3$. Aye, Y. PhD Thesis, Harvard University, **2009**.

Scheme 2.4. Modified first generation retrosynthetic analysis.



1. Malonate Fragment

Preparation of malonate **16** started from 4-vinyl-1,3-dioxolan-2-one **17**. A palladium catalyzed dynamic kinetic asymmetric transformation[7] of **17** with 2-nitrobenzene-sulfonamide **18** (2-$NsNH_2$) afforded key chiral building block **19**, which was then enantioenriched via recrystallization. *N*-alkylation of **19** with 1-iodo-5-hexene generated **20** in high yield. The primary alcohol was then transformed into the triflate,[8] and substitution by dimethyl malonate afforded compound **21**. Removal of Ns group with PhSH and *in situ* lactamization gave diene **22**. Ring closing metathesis of diene **22** with Grubbs first generation catalyst[9] afforded the desired fragment **16** in high yield (Scheme 2.5).

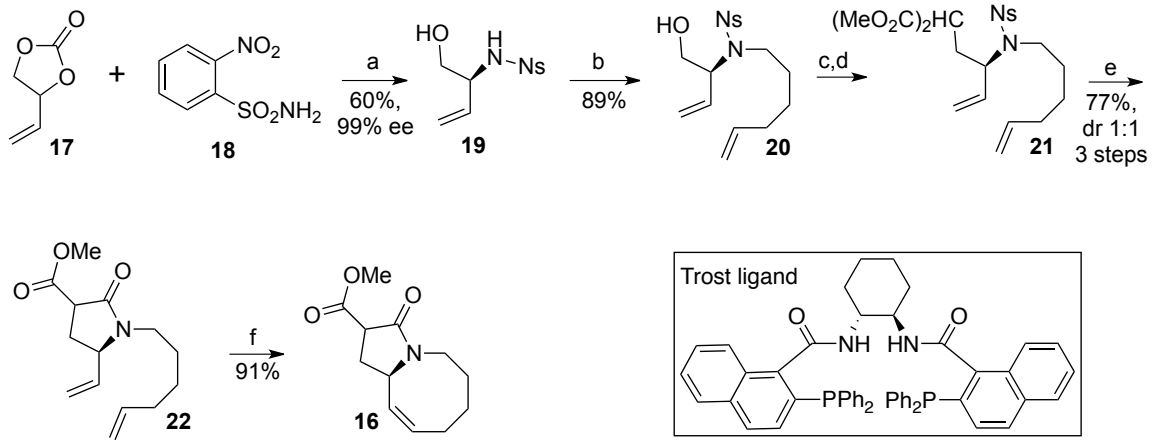
---

[7] Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976. Carbonate **17** was used instead of the more expensive 3,4-epoxy-1-butene and 2-$NsNH_2$ (**18**) was employed as a new nitrogen nucleophile instead of phthalimide to increase the overall efficiency of the route. 2-$NsNH\text{-}(CH_2)_4CHCH_2$ and 4-$NsNH_2$ were also investigated, but gave lower *ee*.

[8] The corresponding iodide, tosylate are not reactive enough for this substitution reaction.

[9] RCM of substrates such as **20** and **21** failed with Grubbs first generation catalyst. Use of Grubbs second generation catalyst did provide the desired RCM product, however, the yield was lower than that observed with **22**.

Scheme 2.5. Preparation of malonate **16**.

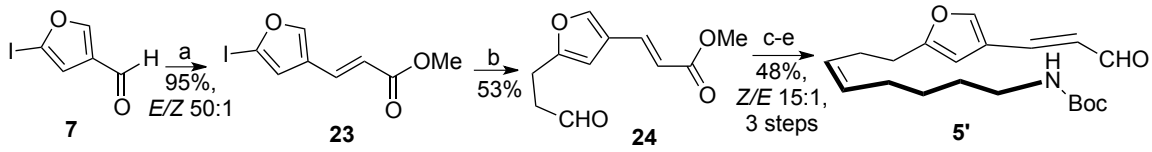


Reagents and conditions: (a) $(PdC_3H_5Cl)_2$ (1 mol%), (*R,R*)-DACH-naphthyl Trost ligand (2.5 mol%), Na_2CO_3 (5 mol%), 83% yield, 80% ee; recrystallized to 60% yield, > 99% ee; (b) 1-iodo-5-hexene, K_2CO_3, DMF, 89%; (c) Tf_2O, pyridine; (d) $LiCH(CO_2Me)_2$; (e) PhSH, K_2CO_3, DMF, 77% (3 steps), dr ~1:1; (f) Grubbs first generation catalyst (2 × 1 mol%), DCM (2 mM), 91%, dr ~1:1. Ns = 2-nitrobenzenesulfonyl.

2. Furan Fragment

The enal fragment **5′** was prepared from aldehyde **7** in five steps. A Horner-Wadsworth-Emmons olefination reaction of **7** with $(MeO)_2(O)PCH_2CO_2Me$ gave unsaturated ester **23**. Heck coupling of **23** with allyl alcohol provided aldehyde **24**. Wittig olefination of **24** with ylide derived from $BocHN(CH_2)_5PPh_3I$ installed the cis-olefin, and subsequent redox chemistry on the ester gave enal **5′** (Scheme 2.6).

Scheme 2.6. Preparation of enal.

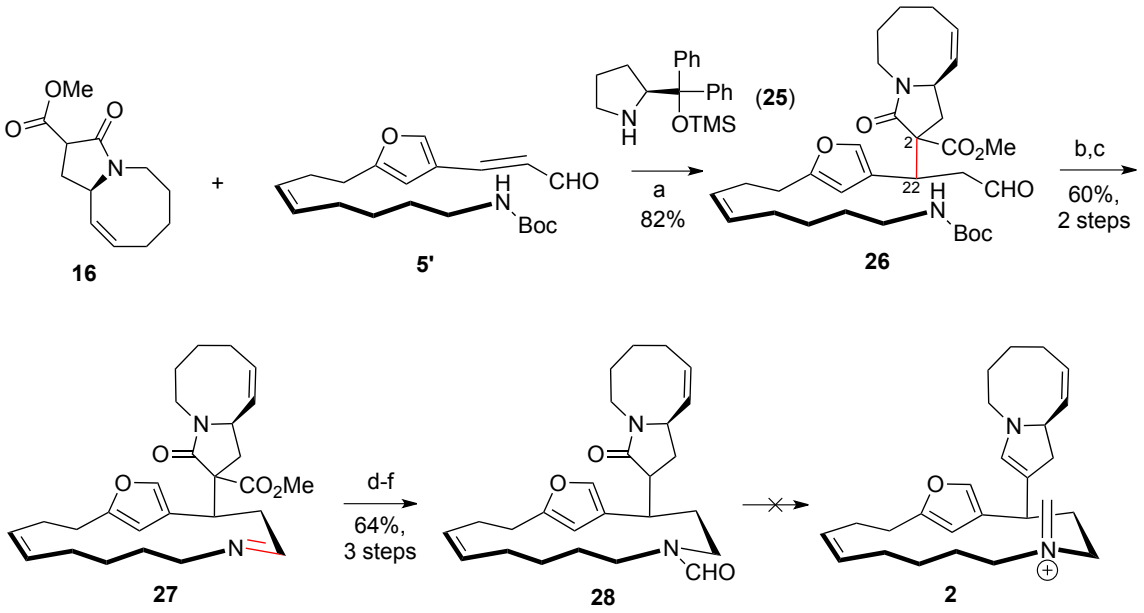


Reagents and conditions: (a) NaHMDS, $(MeO)_2(O)PCH_2CO_2Me$, *E/Z* > 50:1, 95%; (b) $Pd(OAc)_2$, $NaHCO_3$, $(Bu)_4NBr$, allyl alcohol, 53%; (c) KHMDS, $BocHN(CH_2)_5PPh_3I$, *Z/E*~15;1, 62%; (d) DIBAL-H, (80%); (e) $BaMnO_4$, 96%.

3. Fragment Coupling

Malonate **16** and enal **5′** underwent a Michael addition reaction in the presence of Jørgensen–Hayashi catalyst (**25**) (Scheme 2.7). [10] The Michael adduct **26** was obtained in good yield and good selectivity at the tertiary center, but quite surprisingly, no selectivity at the quaternary center. Since the quaternary center will be destroyed as planned, Michael adduct **26** was carried on as a mixture of diastereomers in the synthesis.

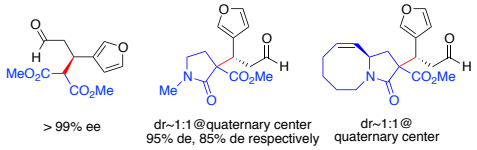
Scheme 2.7. Fragment coupling and attempted cascade precursor synthesis.



Reagents and conditions: (a) **25** (10 mol%), MeOH, 82%, dr 1:1 (C2), 10:1 (C22); (b) $HC(OMe)_3$, HCl, MeOH; (c) 1,2-dichloroethane, 60 °C , 60%, (2 steps); (d) $NaBH(OAc)_3$; (e) HCOOAc; (f) DMSO, NaCl, 190 °C, 64% (3 steps).

---

[10] Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2006,** 45, 4305-4309. The Michael addition reaction was first studied in a model system with Jørgensen–Hayashi catalyst. Good selectivity was obtained in the tertiary center, however, no selectivity was observed in the quaternary center.

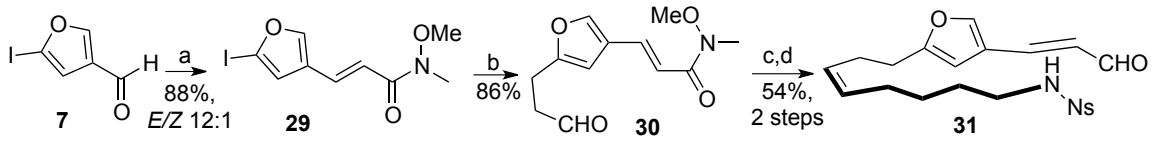


Following the removal of Boc protecting group, the macrocycle **27** was obtained by imine formation; the two major diastereoisomers were separated and characterized at this stage. The macrocycle imine **27** was reduced and transformed into a formamide. Krapcho decarboxylation of the malonate gave bisamide **28** as a 1:1 mixture of rotamers. The transformation of **28** into the cascade precursor **2** was investigated with a variety of reducing reagents. No desired product was obtained.

IV. A Formal Total Synthesis of (–)-Nakadomarin A

Since the product from the Michael addition reaction possesses the complete carbon framework of the natural product, a total synthesis of (–)-nakadomarin A was developed. The enal fragment **31** with Ns protecting group on amine was used as the Michael acceptor (Scheme 2.8). Wittig olefination of aldehyde **7** with ylide $Ph_3PCHCONMe(OMe)$[11] gave unsaturated Weinreb amide **29**. Heck coupling reaction of **29** with allyl alcohol provided aldehyde **30**, Wittig olefination of the aldehyde and reduction of Weinreb amide afforded enal **31**.

Scheme 2.8. Preparation of enal **31**.



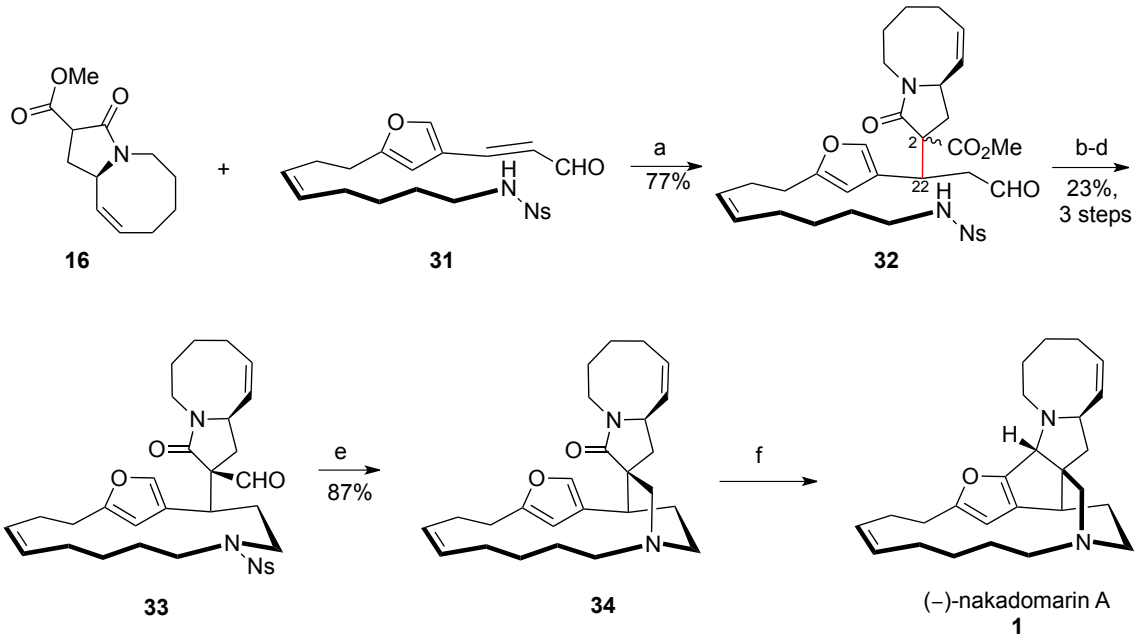
Reagents and conditions: (a) $Ph_3PCHCONMe(OMe)$, 88%, *E/Z* 12:1; (b) $Pd(OAc)_2$, $NaHCO_3$, $(Bu)_4NBr$, allyl alcohol, DMF, 86%; (c) KHMDS, $NsHN(CH_2)_5PPh_3I$, THF, 64%, *Z/E*~10:1; (d) DIBAL-H, 84%.

Michael reaction product **32** was obtained as a ~1:1 mixture of diastereoisomers from malonate **16** and enal **31** (Scheme 2.9). Aldehyde **32** was reduced to a primary alcohol by

[11] Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

$NaBH(OAc)_3$, subsequent Fukuyama-Mitsunobu alkylation with PPh_3 and diethyl azodicarboxylate (DEAD) generated the macrocycle. Reduction of the malonate ester with DIBAL-H at low temperature stopped at the aldehyde stage. The resultant two diastereoisomers were separable via preparative TLC, and provided the desired analytically pure aldehyde **33**. The Ns group was then removed with PhSH, and reductive amination with $NaBH(OAc)_3$ formed the 6-membered ring of the known compound **34**.[12] Amide activation with Tf_2O, and cyclization with the furan ring, followed by $NaBH_4$ reduction generated the natural product (–)-nakadomarin A.

Scheme 2.9. Formal total synthesis of (–)-nakadomarin A.



Reagents and conditions: (a) **25** (15 mol%), MeOH, 77%, dr 1:1 (C2), 10:1 (C22); (b) $NaBH(OAc)_3$; (c) PPh_3, DEAD; 78%, 2 steps; (d) DIBAL-H, separation of diastereomers, 30%; (e) PhSH, K_2CO_3; then $NaBH(OAc)_3$, 87%; (f) see ref 11. Tf_2O, 2,6-ditert-butyl-4-methylpyridine, then $NaBH_4$, MeOH.

[12] Jakubec, P.; Kyle, A.F; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011***, 52,* 6094-6097.

V. Experimental Section

General Information

Reactions in anhydrous solvents were conducted under an atmosphere of nitrogen or argon in glassware that was flame-dried or oven-dried. Analytical thin layer chromatography (TLC) was performed on EMD Reagent 0.25 mm silica gel 60 F254 plates. Visualization was accomplished with UV light (254 nm) followed by heating after staining the plate with ceric ammonium molybdate solution, unless otherwise noted. Extraction and chromatography solvents were reagent grade or HPLC grade, and were used without further purification. Product purification was performed by flash column chromatography using Sorbent Technologies silica gel (40–63 μm, 230–400 mesh).

Analytical Information

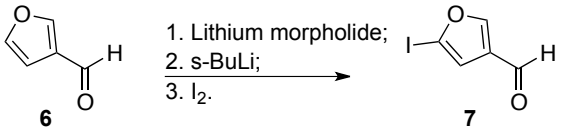
Unless otherwise stated, all isolated and characterized compounds were >95% pure as judged by ^{1}H NMR spectroscopic analysis. ^{1}H NMR spectra were recorded at room temperature on a Varian Inova 600 spectrometer (600 MHz), a Varian Inova 500 spectrometer (500 MHz), or a Mercury 400 spectrometer (400 MHz). ^{1}H NMR data are reported in the following format: chemical shift (multiplicity, coupling constants, integration). Chemical shifts are reported in ppm with the residual solvent resonance as internal standard (7.26 ppm for $CDCl_3$, 7.16 ppm for C_6D_6, 3.34 ppm for CD_3OD). Multiplicity is abbreviated as follows: m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, oct = octet, br = broad, app = apparent. Proton assignments were made with the aid of 2D-COSY experiments or homo-nuclear decoupling experiments. ^{13}C NMR spectra were recorded at room temperature on a Varian Inova 500 spectrometer (125 MHz), or a Mercury 400 spectrometer (100 MHz)

with broadband proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as internal standard (77.0 ppm for $CDCl_3$, 128.0 ppm for C_6D_6, 49.9 ppm for CD_3OD). Carbon assignments, when made, were made with the aid of 2D-HSQC. Infrared spectra were recorded as thin films on NaCl plates using a Perkin Elmer 1600 series FT-IR spectrometer at a resolution of 4 cm^{-1}. Optical rotations were measured on a Jasco DIP-181 digital polarimeter with a sodium lamp, and are reported as: $[\alpha]^{T(^{\circ}C)}_{D}$ XX° (*c* (g/100 mL), solvent). Melting points were measured on a MEL-TEMP® II capillary melting point apparatus and are uncorrected. High-resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers at the Harvard University Mass Spectrometry Laboratory. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series HPLC with a diode array multiple wavelength detector, or on an Agilent 1100 Series HPLC equipped with a variable wavelength detector, using the indicated chiral column and eluent.

Materials

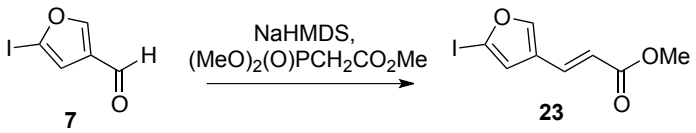
Tetrahydrofuran, diethyl ether, toluene and dichloromethane employed as reaction solvents were dried by passage through a column of activated alumina under an argon atmosphere. Amine bases (triethylamine, pyridine, morpholine) were distilled from calcium hydride prior to use. EMD DriSolv dimethyl sulfoxide and *N,N*-dimethylformamide were used without further purification. Organolithium reagents (e.g. *n*-butyllithium, *s*-butyllithium, etc.) were purchased from commercial suppliers and were titrated prior to use by standard literature methods.

Experimental Procedures

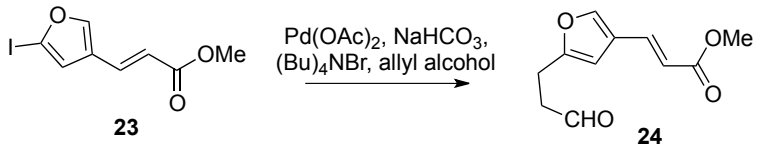


5-iodofuran-3-carbaldehyde (**7**).[13] To a solution of morpholine (4.40 mL, 50.5 mmol) in THF (375 mL) at –78 °C was slowly added a solution of *n*-BuLi (20.2 mL, 2.5 M in hexanes, 50.5 mmol) via syringe. After stirring for 15 min at this temperature, 3-furancarboxaldehyde (4.30 mL, 49.7 mmol) was added via syringe. After stirring for another 15 min, *s*-BuLi (36.5 mL, 1.4 M in cyclohexane, 51.1 mmol) was added slowly via syringe. The resulting solution was stirred for 3 h at this temperature, after which time a solution of I_2 (13.1 g, 51.6 mmol) in THF (20 mL) was added via cannula until the color persisted. $Na_2S_2O_3$ (sat.) was added and the mixture was warmed to room temperature. The solvent was removed under reduced pressure and the residue was extracted with diethyl ether. The extracts were dried over Na_2SO_4 and concentrated. ^{1}H NMR analysis of the residue showed ~ 5:1 (C5:C2) regioselectivity. Purification by flash column chromatography with 2-3% EtOAc in hexanes afforded the product as an off-white solid (6.17 g, 27.8 mmol, 56%). The product is a crystalline solid and stable for months when stored in a –20 °C freezer. It is less stable in solution under air, especially in chlorinated solvents. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** (C_6D_6, 600 MHz) δ 9.19 (s, 1H), 6.91 (s, 1H), 6.57 (s, 1H). **^{13}C NMR** (C_6D_6, 125 MHz) δ 181.8, 154.6, 131.1, 117.6, 92.1. **Mp**: 43–45°C. **IR** (C_6D_6 film): 3136, 2827, 2729, 1694 cm^{-1}.

[13] Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126-3131.



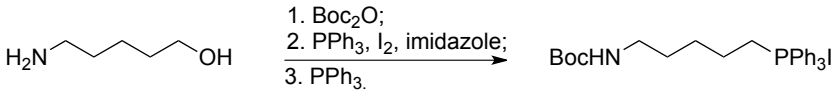
(*E*)-methyl 3-(5-iodofuran-3-yl)acrylate (**23**). A solution of NaHMDS (1.35 mL, 1.0 M solution in THF, 1.35 mmol) was slowly added to a solution of 5-iodo-3-furancarboxaldehyde (0.253 g, 1.14 mmol) and trimethyl phosphonoacetate (0.28 g, 1.54 mmol) in THF (5 mL) at –78 °C. The solution was warmed to 0 °C and stirred for 20 min, then concentrated and extracted with diethyl ether. Filtration through silica gel and concentration gave the pure product as a white solid (303 mg, 1.09 mmol, 95%). ^{1}H NMR analysis showed ≥ 50:1 *E/Z* selectivity. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.48 (d, *J* = 16.2 Hz, 1H), 6.74 (s, 1H), 6.12 (d, *J* = 16.2 Hz, 1H), 3.78 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.1, 148.7, 133.3, 125.4, 118.5, 117.9, 91.0, 51.7. **Mp**: 58–60 °C. **IR** (CH_2Cl_2 film): 3128, 1641 cm^{-1}.



(*E*)-methyl 3-(5-(3-oxopropyl)furan-3-yl)acrylate (**24**).[14] To a stirring mixture of the iodide **23** (303 mg, 1.09 mmol), Bu_4NBr (354 mg, 1.10 mmol), $NaHCO_3$ (274 mg, 3.26 mmol) and allyl alcohol (0.5 mL, 7 mmol, ~ 7 eq.) in DMF (0.5 mL) was added $Pd(OAc)_2$ (7.0 mg, 0.031 mmol, 2.8 mol%). The mixture was heated in an oil bath at 40 °C for 24 h and then cooled to room temperature. Water was added and the reaction mixture was extracted with Et_2O, the combined organic layers were washed with brine

[14] Jeffery, T. *Tetrahedron Lett.* **1991**, 32, 2121.

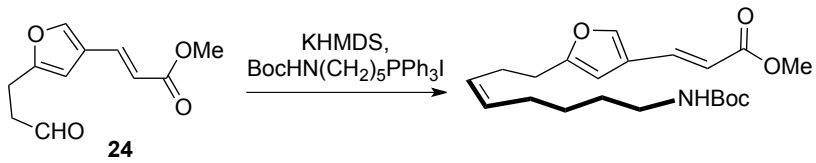
and concentrated. Purification by flash column chromatography with 20% EtOAc in hexanes gave aldehyde **24** (120 mg, 0.58 mmol, 53%) as oil, which solidifies when stored in the freezer. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.80 (br s, 1H), 7.49 (s, 1H), 7.47 (d, *J* = 15.8 Hz, 1H), 6.21 (s, 1H), 6.07 (d, *J* = 15.8, Hz, 1H), 3.74 (s, 3H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 200.3, 167.3, 156.0, 143.4, 134.8, 123.3, 117.1, 103.3, 51.5, 41.4, 20.5. **IR** (CH_2Cl_2 film): 3056, 2953, 2848, 1715, 1644, 1436 cm^{-1}. **HRMS-ESI**: calculated for $[C_{11}H_{12}O_4+H]^+$: 209.0808; found 209.0806.



5-(*tert*-butoxycarbonylamino)pentan-1-triphenylphosphonium iodide. A solution of 5-amino-1-pentanol (5.01 g, 48.6 mmol) and di-tert-butyl dicarbonate (10.9 g, 50 mmol) in DCM (100 mL) was stirred for 3h at 0 °C to rt. A homogenous solution was obtained. The reaction mixture was then cooled to 0 °C, PPh_3 (17 g, 64.9 mmol), imidazole (4.80 g, 70.6 mmol) and I_2 (13.6 g, 53.5 mmol) were added. After stirring 3h at 0°C, the solvent was removed under vacuum and the residue was extracted with diethyl ether and filtered through Celite. The filtrate was concentrated and filtered through silica gel and eluted with 50% diethyl ether in hexanes to afford the iodide, which was contaminated with some PPh_3 and used without further purification.

The iodide and PPh_3 (13.0 g) was refluxed in toluene (20 mL) in a 120 °C oil bath for 5h until no iodide left, and the phosphonium salt precipitated from the solution. The reaction mixture was cooled to rt, then 0 °C and filtered, the white solid product was washed with diethyl ether and dried under vacuum (24.5 g, 42.6 mmol, 87.7%). **^{1}H NMR**

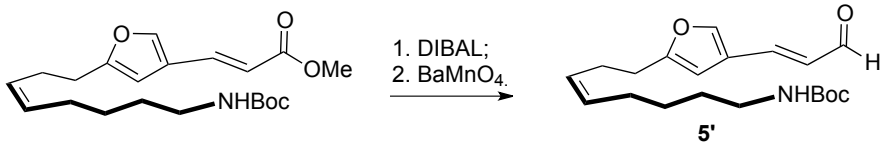
($CDCl_3$, 400 MHz) δ 7.61-7.74 (m, 15H), 4.85 (bs, 2H), 3.50 (bs, 2H), 2.96 (m, 2H), 1.60 (m, 4H), 1.46 (m, 2H), 1.30 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.85, 134.90 (d, J = 2.3 Hz), 133.33 (d, J = 10 Hz), 130.31 (d, J = 12 Hz), 117.63 (d, J = 85.9 Hz), 78.50, 39.43, 28.87, 28.12, 27.05 (d, J = 16 Hz), 22.69 (d, J = 50.6 Hz), 21.74. **IR** (film): 3451, 3316, 3059, 2979, 2935, 2867, 1698, 1510 cm^{-1}. **HRMS-ESI**: calculated for $C_{28}H_{35}NO_2P$ 448.2400, found 448.2419.



24

(*E*)-methyl 3-(5-((*Z*)-8-((*tert*-butoxycarbonyl)amino)oct-3-en-1-yl)furan-3-yl)acrylate. To a stirring suspension of (5-((*tert*-butoxycarbonyl)amino)pentyl)triphenyl-phosphonium iodide (215 mg, 0.374 mmol, 1.3 equiv) in THF (4 mL) at 0 °C was added KHMDS (146 mg, 0.734 mmol, 2.5 equiv), and resulted in a homogenous dark red solution. A solution of aldehyde **24** (60 mg, 0.29 mmol) in THF (4 mL) was added to the Wittig reagent solution via cannula. The mixture was stirred for 40 min until TLC (20% EtOAc in hexanes) indicated completion of the reaction. The reaction mixture was quenched with HOAc dropwise until the color turned grey, and then was concentrated. The residue was dissolved in a small amount of DCM and loaded on a silica gel column; purification by gradient elution with 20–30% EtOAc in hexanes gave the product (67 mg, 62%) as an oil. ^{1}H NMR analysis showed ~15:1 *Z/E* ratio. The minor isomer can be further removed by silica gel column impregnated with $AgNO_3$. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **IR** (CH_2Cl_2 film): 3450, 3055, 2984, 2933, 1714, 1644, 1506 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.53 (d, *J* = 15.1 Hz, 1H), 7.51 (s, 1H), 6.19 (s, 1H), 6.08 (d,

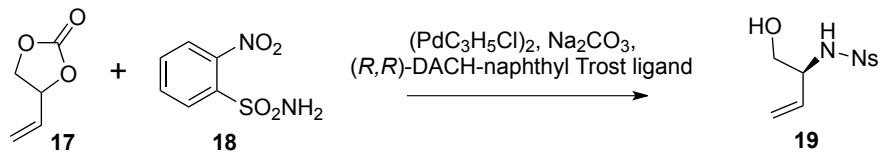
J = 16.1 Hz, 1H), 5.38 (m, 2H), 4.51 (bs, 1H), 3.76 (s, 3H), 3.09 (m, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.37 (app q, *J* = 6.5 Hz, 2H), 2.02 (app q, *J* = 6.9 Hz, 2H), 1.45 (m, 2H), 1.43 (s, 9H), 1.33 (quint, *J* = 7.5 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.5, 157.9, 155.9, 143.3, 135.3, 130.7, 128.1, 123.3, 116.8, 102.8, 79.0, 51.5, 40.4, 29.7, 28.4, 28.0, 26.8, 26.7, 25.5. **HRMS-ESI**: calculated for $[C_{21}H_{31}NO_5+Na]^+$ 400.2094; found 400.2096.



***tert*-butyl ((*Z*)-8-(4-((*E*)-3-oxoprop-1-en-1-yl)furan-2-yl)oct-5-en-1-yl)carbamate (5′)**. To a solution of ester (1.48 g, 0.392 mmol) in DCM (20 mL) at –78 °C was added a solution of DIBAL-H (1 M in hexane, 10.0 mL, 10.0 mmol, ~ 2.5 eq.) dropwise. The solution was warmed to 0 °C and stirred for 30 min. Methanol (1 mL) was added to the solution slowly, followed by H_2O (1 mL). The mixture was stirred at room temperature vigorously for 30 min and filtered through Celite®. The filter cake was rinsed with excess methanol, and the combined filtrate was concentrated. The residue was purified by flash column chromatography with 20–30% EtOAc in hexanes, affording allylic alcohol (1.10 g, 0.315 mmol, 80%) as an oil. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **IR** (CH_2Cl_2 film) 3454, 3008, 2980, 2934, 2861,1698, 1506 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.28 (s, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 6.15 (s, 1H), 6.04 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.38 (m, 2H), 4.57 (bs, 1H), 4.23 (bs, 2H), 3.08 (bs, 2H), 2.64 (t, *J* = 6.9 Hz, 2H), 2.36 (m, 2H), 2.00 (m, 2H), 1.44 (s, 9 H), 1.44 (m, 2H), 1.31 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 156.7, 156.0, 139.0, 130.6, 128.4, 127.8, 124.3, 121.3, 103.1, 79.1, 63.5, 40.5, 29.6, 28.4,

28.0, 26.8, 26.8, 25.7. **HRMS-ESI**: calculated for $[C_{20}H_{31}NO_4+Na]^+$ 372.2145; found 372.2128.

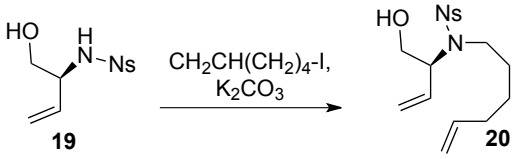
To a solution of allylic alcohol (1.10 g, 3.15 mmol) in DCM (24 mL) was added $BaMnO_4$ (4.0 g, 15.6 mmol, ground into fine powder and dried overnight in the oven before use). The suspension was stirred at room temperature for 6 h and TLC (30% EtOAc/hexanes) showed complete conversion. The reaction mixture was filtered through packed Celite® and rinsed with excess EtOAc. The combined filtrate was concentrated and the residue was purified by flash column chromatography with 30% EtOAc in hexanes, affording the enal (1.05 g, 3.02 mmol, 96%) as an oil. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **IR** (CH_2Cl_2 film): 3446, 3054, 2980, 2933, 2860, 1708, 1678, 1634,1508 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.60 (d, *J* = 7.9 Hz, 1H), 7.62 (s, 1H), 7.34 (d, *J* = 15.5 Hz, 1H), 6.37 (dd, *J* = 15.5, 7.9 Hz, 1H), 6.22 (s, 1H), 5.38 (m, 2H), 4.51 (bs, 1H), 3.09 (app q, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.0 Hz, 2H), 1.45 (m, 2H), 1.43 (s, 9H), 1.33 (app quint, *J* = 7.5 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.4, 158.4, 155.9, 144.1, 142.9, 130.8, 128.1, 128.0, 123.5, 102.9, 79.0, 40.4, 29.6, 28.4, 27.9, 26.8, 26.7, 25.4. **HRMS-ESI**: calculated for $[C_{20}H_{29}NO_4+Na]^+$ 370.1989; found 370.1983.



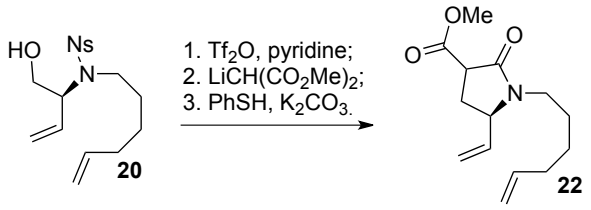
(*S*)-*N*-(1-hydroxybut-3-en-2-yl)-2-nitrobenzenesulfonamide (**19**). [15] 2-Nitrobenzene-sulfonamide (2.02 g, 10 mmol), $[Pd(C_3H_5)Cl]_2$ (36.5 mg, 0.1 mmol, 1.0 mol%), N,N'-bis(2-diphenylphosphino-1-naphthoyl)-(1*R*,2*R*)-(-)-1,2-diaminocyclohexane (202 mg, 0.255 mmol, 2.55 mol%) and Na_2CO_3 (53 mg, 0.5 mmol, 5 mol%) were mixed in a round bottom flask and evacuated/backfilled with nitrogen for three cycles. DCM (100 mL) was added via syringe and the suspension was stirred for 10 min. 4-Vinyl-1,3-dioxolan-2-one (1.20 mL, 12.4 mmol, 1.24 eq.) was added via syringe and the mixture was stirred for 3 h, by which time the reaction mixture became clear and TLC (30% EtOAc in hexanes) showed complete consumption of 2-$NsNH_2$. The solution was loaded on a silica gel column, and eluted with 0–50% EtOAc in hexanes to give the product (2.27 g, 8.34 mmol, 83%, 80% ee) as a white solid. The enantiomeric excess of the product was determined by HPLC: ODH column, 85:15 i-PrOH/hexanes, 1.0 mL/min, 254 nm, τ(minor) = 17.9 min, τ(major) = 20.0 min. The optical purity of the product was increased by recrystallization from toluene (1.70 g, 62%, >99% ee). The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **Mp**: 95–97 °C. **$[\alpha]^{23}_D$** = 79.8 (*c* 1.10, EtOAc). **IR** (CH_2Cl_2 film): 3361, 3054, 2987, 1543, 1422, 1360 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.11 (m, 1H), 7.87 (m, 1H), 7.73 (m, 2H), 5.81(bs, 1H), 5.67 (dddd, *J* = 17.0, 10.5, 6.4, 2.3 Hz, 1H), 5.17 (app d, *J* = 17 Hz, 1H), 5.09 (app d, *J* = 10.5 Hz, 1H), 4.10 (m, 1H), 3.70 (dddd, *J* = 11.0, 7.0, 4.4, 2.3 Hz, 1H), 3.63 (app dtd, *J* = 10.8, 5.6, 2.3 Hz, 1H), 2.00 (t, *J* = 6.0 Hz , 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 147.8, 134.5, 133.8, 133.6, 132.8, 131.0, 125.3, 118.3, 64.9, 58.7. **HRMS-ESI**: calculated for $[C_{10}H_{12}N_2O_5S+Na]^+$ 295.0359; found 295.0352.

---

[15] Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.



(*S*)-*N*-(hex-5-en-1-yl)-*N*-(1-hydroxybut-3-en-2-yl)-2-nitrobenzenesulfonamide (**20**). A mixture of the nosylamide **19** (1.54 g, 5.66 mmol), 1-iodo-5-hexene (1.51 g, 7.19 mmol) and K_2CO_3 (1.58 g, 11.4 mmol) in DMF (5 mL) was heated in an oil bath at 60 °C. Additional 5-hexenyl-1-iodide (0.30 g) was added after 12 h. TLC (50% EtOAc in hexanes) and ^{1}H NMR analysis showed completed consumption of starting material after 24 h. The solvent was removed under vacuum in a 60 °C oil bath, and the resulting solid residue was cooled and extracted with EtOAc, and then filtered through Celite®. The filtrate was concentrated and the residue was purified by flash column chromatography with 30% EtOAc in hexanes, affording the product (1.77 g, 5.00 mmol, 88%) as light yellow oil. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. $\mathbf{[\alpha]^{23}_D}$ = 38.7 (*c* 1.58, $CHCl_3$). **IR** (CH_2Cl_2 film): 3543, 3078, 2935, 1539, 1372, 1344 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.09 (m, 1H), 7.69 (m, 2H), 7.62 (m, 1H), 5.74 (m, 2H), 5.25 (app d, *J* = 10.7 Hz, 1H), 5.19 (app d, *J* = 17.6 Hz, 1H), 5.00 (app d, *J* = 17.0 Hz, 1H), 4.95 (app d, *J* = 10.2 Hz, 1H), 4.46 (m, 1H), 3.78 (m, 2H), 3.33 (ddd, *J* = 15.5, 10.5, 5.3 Hz, 1H), 3.25 (ddd, *J* = 15.5, 10.8, 5.6 Hz, 1H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.66 (m, 2H), 1.37 (quint, *J* = 7.6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 147.8, 138.0, 133.5, 133.3, 132.7, 131.6, 130.6, 123.9, 119.3, 114.6, 62.1, 61.2, 44.9, 32.9, 30.2, 25.8. **HRMS-ESI**: calculated for $[C_{16}H_{22}N_2O_5S+Na]^+$ 377.1141; found 370.1143.



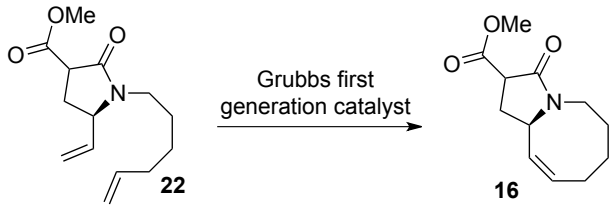
(5*R*)-methyl 1-(hex-5-en-1-yl)-2-oxo-5-vinylpyrrolidine-3-carboxylate (**22**). To a solution of the alcohol **20** (1.77 g, 5.00 mmol) and pyridine (0.66 g, 8.35 mmol) in DCM (20 mL) at –78 °C was added Tf_2O (1.04 mL, 6.16 mmol) dropwise via syringe. The solution was warmed to 0 °C and stirred for 2 h, at which time TLC (30% EtOAc in hexanes) showed complete consumption of starting material. The reaction mixture was loaded on a silica gel column and washed with DCM to give the triflate intermediate, which was carried to the next step without further purification or storage.

In a separate flask, *n*-BuLi (2.87 M in hexanes, 3.0 mL, 8.61 mmol) was added dropwise to a solution of dimethyl malonate (2.1 g, 16 mmol) in THF (10 mL) at –78 °C. The solution was warmed to 0 °C and transferred via cannula to a solution of the triflate in THF (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 h and concentrated, filtered through silica gel and eluted with EtOAc to give the malonate product (contained dimethyl malonate) and used without further purification. A small amount of malonate was purified for analytical purpose. The analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. $\mathbf{[\alpha]^{23}_D}$ = 49.9 (*c* 1.08, $CHCl_3$). **IR** (CH_2Cl_2 film): 3055, 2987, 1754, 1736, 1547 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.94 (m, 1H), 7.66 (m, 2H), 7.57 (m, 1H), 5.72 (m, 1H), 5.60 (ddd, *J* = 17.0, 10.3, 5.9 Hz, 1H), 5.14 (app d, *J* = 10.7 Hz, 1H), 5.10 (app d, *J* = 17.0 Hz, 1H), 4.98 (app dq, *J* = 17.1, 2.0 Hz, 1H), 4.93 (app d, *J* = 10.3 Hz, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.62 (app q, *J* = 4.9 Hz, 1H), 3.33 (ddd, *J* = 15.1, 11.2, 5.4 Hz, 1H), 3.10 (ddd, *J*

= 15.1, 10.7, 4.9 Hz, 1H), 2.35 (ddd, *J* = 14.2, 9.3, 5.9 Hz, 1H), 2.05 (ddd, *J* = 14.2, 9.3, 4.9 Hz, 1H), 2.01 (m, 2H), 1.72 (m, 1H), 1.57 (m, 1H), 1.37 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 169.5, 169.0, 147.9, 138.0, 134.6, 133.6, 133.1, 131.5, 130.8, 123.9, 118.8, 114.7, 57.5, 52.6, 52.5, 47.9, 44.7, 33.0, 31.1, 30.7, 26.0. **HRMS-ESI**: calculated for $[C_{21}H_{28}N_2O_8S+K]^+$ 507.1198; found 507.1217.

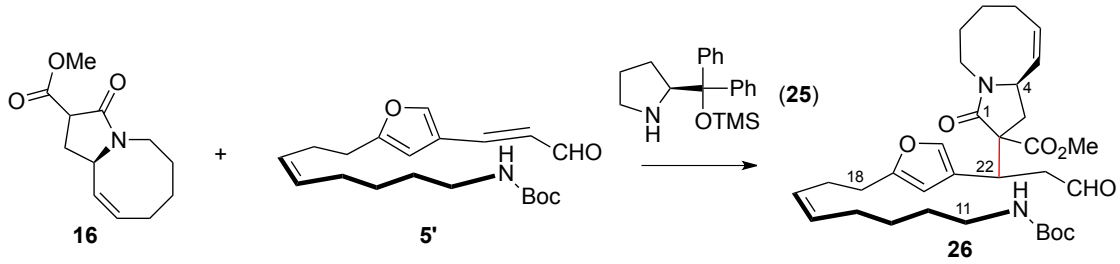
A mixture of malonate (from previous step), K_2CO_3 (2.00 g, 14.5 mmol), and PhSH (0.80 mL, 8.0 mmol) was stirred in DMF (5 mL) at room temperature for 24 h.[16] The volatiles were removed by distillation at 60 °C under vacuum (~1 torr), the residue was extracted with EtOAc and filtered through Celite®. The filtrate was concentrated and purified by flash column chromatography with 20–30% EtOAc in hexanes, affording the lactam product **22** (0.99 g, 79% from alcohol) as an inseparable 1:1 mixture of diastereoisomers. **$[\alpha]^{23}_D$** −53.7 (c 2.04, $CHCl_3$); **IR** (CH_2Cl_2 film): 3055, 2985, 1742, 1686 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.78-5.69 (m, 3H), 5.60 (app quint, *J* = 8.5 Hz, 1H), 5.30-5.23 (m, 4H), 4.99-4.91 (m, 4H), 4.18 (app q, *J* = 7.0 Hz, 1H), 3.97 (app q, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.56 (1H), 3.56 (dt, *J* = 13.5, 6.7 Hz, 1H), 3.51 (dt, *J* = 13.8, 7.0 Hz 1H), 3.44 (m, 2H), 2.93-2.88 (m, 2H), 2.54 (m, 1H), 2.44 (m, 1H), 2.16 (m, 1H), 2.03 (m, 4H), 1.94 (m, 1H), 1.44 (m, 2H), 1.34 (4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.6, 169.5, 169.3, 138.33, 138.27, 137.7, 137.2, 119.1, 118.7, 114.73, 114.67, 60.1, 59.9, 52.61, 52.59, 47.9, 47.7, 40.8, 40.7, 33.18, 33.16, 29.8, 29.2, 26.4, 26.3, 25.9, 25.8. **HRMS-ESI**: calculated for $[C_{14}H_{21}NO_3+Na]^+$ 274.1414; found 274.1424.

[16] Kan, T., Fukuyama, T. *Chem. Comm.*, **2004**, 353-359.



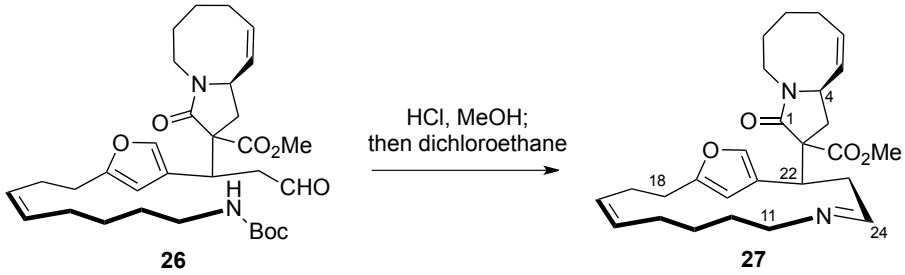
(10a*R*,*Z*)-methyl 3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate (**16**). A solution of diene **22** (0.99 g, 3.94 mmol) in DCM (2.0 L, from a newly opened bottle, reagent grade) was gently refluxed; Grubbs 1st generation catalyst (2 × 32 mg, 0.078 mmol, 2.0 mol%) was added in two portions over 5 h. The reaction mixture was refluxed for 20 h. ^{1}H NMR analysis of an aliquot showed completed reaction. The solution was cooled to room temperature and concentrated. The residue was purified by flash column chromatography with 30–50% EtOAc in hexanes, affording the known bicyclic product[17] (0.81 g, 92%) as a 1:1 mixture of diastereoisomers. $[\alpha]^{23}_{D}$ −94.1 (c 1.22, $CHCl_3$); **IR** (CH_2Cl_2 film): 3020, 2935, 2859, 1740, 1682, 1456, 1435 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.94 (dd, *J* = 10.8, 8.5 Hz , 1H), 5.84 (dd, *J* = 10.8, 8.2 Hz, 1H), 5.46 (dd, *J* = 10.8, 7.0 Hz , 1H), 5.84 (dd, *J* = 10.8, 6.1 Hz, 1H),, 4.45 (app q, *J* = 6.7 Hz, 1H), 4.30 (app q, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.65 (dd, *J* = 14.0, 8.2 Hz, 1H), 3.48 (m, 4H), 3.22 (dd, dd, *J* = 14.3, 8.2 Hz, 1H), 2.62 (ddd, *J* = 14.3, 7.6, 6.7 Hz, 1H), 2.52 (ddd, *J* = 12.9, 9.0, 7.3 Hz, 1H), 2.36-2.25 (m, 2H), 2.21 (ddd, *J* = 12.9, 9.0, 7.6 Hz, 1H), 2.16 (m, 2H), 2.01 (ddd, *J* = 12.9, 8.8, 4.9 Hz, 1H), 1.94 (m,1H), 1.84 (m, 1H), 1.66 (m, 3H), 1.51 (m, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.2 (2C), 168.7, 168.5, 134.0,131.8, 129.5, 128.5, 54.9, 53.9, 52.1, 48.4, 47.8, 41.1, 40.8, 30.1, 29.7, 26.9, 26.5, 25.6, 25.0, 24.6.

[17] Jakubec. P.; Cockfield, D.; Dixon, D.; *J. Am. Chem. Soc.*, **2009**, *131*, 16632.



(10a*R*,*Z*)-methyl 2-((*S*)-1-(5-((*Z*)-8-((*tert*-butoxycarbonyl)amino)oct-3-en-1-yl)furan-3-yl)-3-oxopropyl)-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate (**26**). A solution of malonate **16** (23 mg, 0.10 mmol), enal **5′** (41 mg, 0.12 mmol) and (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**25**) (3.1 mg, 0.010 mmol, 0.10 mol%) in MeOH (0.15 mL) was stirred at room temperature for 3 days. The solution was concentrated and the residue was purified by flash column chromatography with 30–40% EtOAc in hexanes gave the product (50 mg, 88%) as an inseparable 1:1 mixture of diastereoisomers. **IR** ($CDCl_3$ film): 3444, 3054, 2986, 2931, 2858, 1728, 1714, 1694, 1682 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.56 (m, $C_{24}H$, 2H), 7.18 (s, ArH, 1H), 7.13 (s, ArH, 1H), 5.96 (s, ArH, 1H), 5.88 (s, ArH, 1H), 5.77 (m, C_6H, 2H), 5.32 (m, $1C_5H$, $2C_{15}H$, $2C_{16}H$, 5H), 5.18 (m, $1C_5$, 1H), 4.58 (br, NH, 2H), 4.26 (m, $1C_4H$, $1C_{22}H$, 2H), 3.89 (dd, J = 13, 3.2 Hz, $C_{22}H$, 1H). 3.75 (s, CH_3O, 3H), 3.73 (s, CH_3O, 3H), 3.69 (m, C_4H, 1H), 3.45(m, 2H), 3.30 (m, 2H), 3.22 (m, 1H), 3.09 (m, 5H), 3.02 (m, 1H), 2.81 (dd, J = 20, 3.0 Hz, 1H), 2.63 (dd, dd, J = 15.6, 8.4 Hz, 1H), 2.59-2.49 (m, 7H), 2.35 (dd, J = 16.8, 10 Hz, 1H), 2.28 (m, 6H), 2.18 (dd, J = 16, 7.2 Hz, 1H), 2.00 (m, 4H), 1.87 (m, 3H), 1.76 (dd, J = 16, 10 Hz, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.50-1.45 (m), 1.42 (s, 9H), 1.32 (m, 4H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 201.02, 200.97, 172.4, 171.0, 170.3, 169.7, 156.8, 156.2, 140.1, 139.3, 134.6, 133.0, 130.8, 130.6, 129.8, 128.6, 128.5, 123.2, 122.9, 107.4, 105.9, 79.1, 61.1, 59.1, 54.0, 53.2, 52.9, 45.7, 44.2,

42.2, 42.0, 40.7, 35.9, 35.2, 34.2, 29.9, 28.6, 28.3, 28.2, 27.5, 27.2, 27.00, 26.95, 25.7, 25.7, 25.5. **HRMS-ESI**: calculated for $[C_{32}H_{46}N_2O_7+H]^+$ 571.3378; found 571.3399.



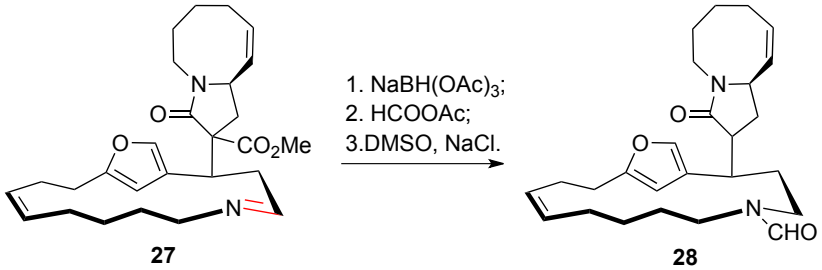
26 **27**

Macrocyclic imine 27. To a solution of Michael product **26** (25 mg, 0.044 mmol) in $HC(OMe)_3$ (0.10 g, 0.9 mmol) and MeOH (0.20 g, 6.3 mmol) at 0 °C, was added AcCl (0.12 mL, 1.7 mmol) dropwise. The solution was warmed to room temperature and stirred for 3 h, at which time TLC (50% EtOAc in hexanes) showed complete conversion of the starting material. The solution was then cooled to −78 °C, and excess HCl was removed by high vacuum over 2 h with a liquid nitrogen trap. The solvent was then removed under vacuum by slowly warming the cooling bath to room temperature. The residue was dried under high vacuum overnight and dissolved in 1,2-dichloroethane (5 mL). The solution was heated in an oil bath at 60 °C for 8 h under nitrogen and at the end was concentrated to about half volume by distillation under slight vacuum at the same temperature. Saturated $NaHCO_3$ was added and the solution was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography with 60−100% EtOAc in hexanes afforded two major macrocyclic imine products. Stereochemistry of the quaternary center is not determined. The isolated yield and analytical data are reported for material judged ~90% pure as determined by ^{1}H NMR spectroscopy.

Less polar one (6.0 mg, 31%) $[\alpha]^{23}_{D}$ −34.9 (c 0.68, $CHCl_3$); **IR** ($CHCl_3$ film): 3020, 2932, 2857, 1733, 1674 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.32 (d, *J* = 8.3 Hz, $C_{24}H$, 1H), 7.16 (s, ArH, 1H), 5.92 (s, ArH, 1H), 5.75 (app q, *J* = 9.2 Hz, C_6H, 1H), 5.37 (app q, *J* = 9.0 Hz, $C_{15}H$, 1H), 5.22 (m, C_5H, $C_{16}H$, 2H), 4.24 (app q, *J* = 7.2 Hz, C_4H, 1H), 4.02 (dd, *J* = 12.7, 2.9 Hz, $C_{23}H$, 1H), 3.79 (s, CH_3O, 3H), 3.76 (m, $C_{11}H$, 1H), 3.24 (bs, $C_{10}H$, 2H), 2.82 (m, $C_{11}H$, 1H), 2.67 (dd, *J* = 12.7, 6.8 Hz, C_3H, 1H) 2.64 (m, $C_{18}H$, 1H), 2.49-2.39 (m, $C_{17}H$, $C_{18}H$, $C_{22}H$, 3H), 2.32 (td, *J* = 12.7, 8.3 Hz, $C_{23}H$, 1H), 2.09 (m, $C_{17}H$, 1H), 1.86 (dd, *J* = 12.9, 8.8 Hz, C_3H, 1H), 1.81-1.42 (m, C_7H, C_8H, C_9H, $C_{12}H$, $C_{14}H$, 10H), 0.65 (m, $C_{13}H$, 1H), 0.12 (m, $C_{13}H$, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.1, 169.5, 162.8, 154.6, 141.1, 134.4, 131.2, 128.5, 127.4, 121.2, 109.4, 61.4, 61.0, 54.8, 52.9, 42.0, 37.0, 36.3, 31.5, 29.4, 27.6, 27.3, 27.0, 26.9, 26.3, 24.9. **HRMS-ESI**: calculated for $[C_{27}H_{36}N_2O_4+Na]^+$ 475.2567; found 475.2584.

More polar one (5.3 mg, 28%) $[\alpha]^{23}_{D}$ −75.9 (c 0.56, $CHCl_3$); **IR** ($CHCl_3$ film): 3054, 2929, 1732, 1674 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.29 (d, *J* = 7.8 Hz, $C_{24}H$, 1H), 7.13 (s, ArH, 1H), 5.85 (s, ArH, 1H), 5.79 ("q", *J* = 9.2 Hz, C_6H, 1H), 5.44 ("q", *J* = 9.0 Hz, $C_{15}H$, 1H), 5.39 (dd, *J* = 10.8, 6.8 Hz, C_5H, 1H), 5.30 (td, *J* = 10.2, 6.6 Hz, $C_{16}H$, 1H), 3.99 ("q", *J* = 6.6 Hz, C_4H, 1H), 3.84 (dd, *J* = 12.6, 3.0 Hz, $C_{23}H$, 1H), 3.72 (s, CH_3O, 3H), 3.64 (m, $C_{11}H$, 1H), 3.55 (dd, *J* = 13.8, 8.4 Hz, $C_{10}H$, 1H), 3.30 (dd, *J* = 13.8, 9.0 Hz, $C_{10}H$, 1H), 2.88 (td, *J* = 10.8, 2.4 Hz, $C_{11}H$, 1H), 2.66 (m, $C_{23}H$, 1H), 2.64 (m, $C_{18}H$, 1H), 2.53 (ddd, *J* = 13.8, 10.8, 2.4 Hz, $C_{18}H$, 1H), 2.47 (m, $C_{22}H$, 1H), 2.41 (dd, *J* = 13.6, 8.3 Hz, C_3H, 1H), 2.36 (m, $C_{17}H$, 1H), 2.34 (dd, *J* = 13.6, 5.4 Hz, C_3H, 1H), 2.24 (m, $C_{17}H$, C_7H, 2H), 2.05 (ddd, *J* = 18.0, 9.6, 2.4 Hz, C_7H, 1H), 1.89-1.35 (m, C_8H, C_9H, $C_{12}H$, $C_{14}H$, 8H), 0.64 (m, $C_{13}H$, 1H), 0.15 (m, $C_{13}H$, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz)

δ 171.5, 169.8, 162.8, 155.9, 139.7, 132.7, 130.9, 129.9, 128.0, 122.3, 107.1, 61.1, 60.5, 53.4, 52.7, 41.7, 37.9, 36.4, 32.8, 29.2, 27.9, 27.5, 27.4, 27.1, 26.7, 25.8, 25.4. **HRMS-ESI**: calculated for $[C_{27}H_{36}N_2O_4+Na]^+$ 475.2567; found 475.2585.



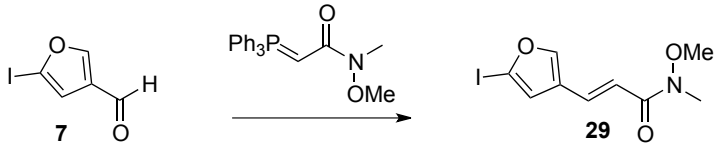
27 **28**

(*Z*)-2-((10a*R*,*Z*)-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocin-2-yl)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-triene-5-carbaldehyde (**28**). A mixture of **27** (43 mg, ~1:1 mixture of diastereoisomers) and $NaBH(OAc)_3$ (30 mg) in DCM (1 mL) was stirred at room temperature for 30 min, then quenched with saturated K_2CO_3 solution, and stirred for another 10 min. The reaction mixture was extracted with DCM, dried over K_2CO_3 and concentrated under vacuum gave the amine product (42 mg, 97% crude yield), which was used in next step without further purification.

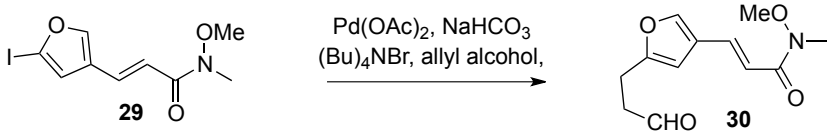
A stock solution of formic acid–acetic anhydride mixture (FAM) was made by heating a mixture of HCOOH (5.15 g, 112 mmol) and Ac_2O (7.20 g, 70.0 mmol) at 60 °C for 2 h. 0.25 g of this solution was added to a solution of macrocyclic amine (18.4 mg) in DCM (0.3 mL). The reaction mixture was stirred for 20 min at room temperature and carefully quenched with saturated K_2CO_3. The aqueous layer was extracted with DCM, organic fraction was dried over solid K_2CO_3 and concentrated under vacuum, affording the *N*-formamide (18.0 mg, 92%) as a 1:1 mixture of rotamers.

The *N*-formamide (18.0 mg) was mixed with NaCl (68 mg), DMSO (0.45 mL) and H_2O (80 mg). The mixture was sealed in a vial and refluxed in a sand bath for 5 h. The solvent

was removed by distillation in a 100 °C oil bath under vacuum. The residue was purified by flash column, eluting with 1%-10% isopropanol/EtOAc, gave bisamide **28** (12.4 mg, 72%, dr ~5:1) as a 1:1 mixture of rotamers on the *N*-formamide. IR (CH_2Cl_2 film): 2936, 2866, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 600M Hz, some diagnostic peaks) δ 8.06 (s) & 8.02 (s), 7.12 (s) & 7.10 (s), 5.95 (s) & 5.94 (s), 5.79 (m, 1H), 5.32 (m, 1H), 5.25 (m, 1H), 5.21 (m, 1H), 4.08 (m, 1H). HRMS (ESI): calculated for $[C_{26}H_{36}N_2O_3+Na]^+$ 447.2618; found 447.2615.

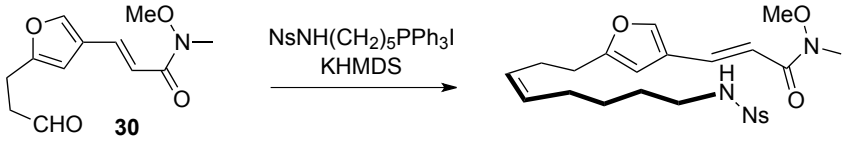


(*E*)-3-(5-iodofuran-3-yl)-*N*-methoxy-*N*-methylacrylamide (**29**). A mixture of aldehyde **7** (573 mg, 2.58 mmol) and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)-acetamide[18] (1.12 g, 3.09 mmol) in DCM (10 mL) was stirred at room temperature for 4h. The solution was loaded onto silica gel column directly and eluted with 30-50% EtOAc in hexanes to obtain the product (695 mg, 2.26 mmol, 88%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 7.35 (d, J= 15.7 Hz, 1H), 6.67 (s, 1H), 6.57 (d, J = 15.7 Hz, 1H), 3.58 (s, 3H), 3.12 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.97, 148.27, 131.33, 125.51, 117.62, 116.05, 90.50, 61.44, 32.04. **IR** (film): 3018, 1660, 1614, 1416, 1384, 1215 cm^{-1}. **HRMS-ESI**: calculated for $C_9H_{10}INO_3$+Na 329.9598, found 329.9610.



[18] Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

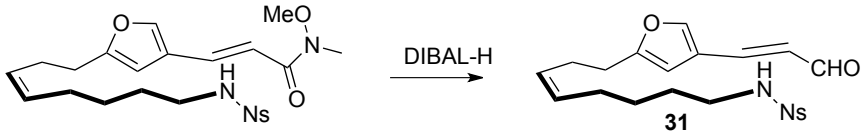
(*E*)-*N*-methoxy-*N*-methyl-3-(5-(3-oxopropyl)furan-3-yl)acrylamide (**30**). To a mixture of iodide **29** (695 mg, 2.26 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), $NaHCO_3$ (381 mg, 4.54 mmol) under nitrogen was added allyl alcohol (0.80 mL, 11.7 mmol) and DMF (6.0 mL). The mixture was stirred at 40 °C oil bath for 15h and no starting material was left as monitored by ^{1}H NMR analysis of an aliquot. The reaction mixture was diluted with half saturated brine and extracted with EtOAc. The organic extracts were combined and dried over Na_2SO_4 and concentrated. Purification by flash column chromatography with 50% EtOAc in hexanes afforded the product (460 mg, 1.94 mmol, 86%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.63 (bs, 1H), 7.36 (s, 1H), 7.35 (d, J =15.7 Hz, 1H), 6.52 (d, J = 15.7 Hz, 1H), 6.13 (s, 1H), 3.56 (s, 3H), 3.09 (s, 3H), 2.78 (t, J = 7.0 Hz, 2H), 2.64 (t, J = 7.0 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 200.17, 166.5, 155.5, 142.96, 132.93, 123.42, 114.75, 103.05, 61.33, 40.99, 31.93, 20.11. **IR** (film): 2968, 2938, 2901, 2826, 2730, 1728, 1660, 1614, 1462, 1416, 1384, 1132 cm^{-1}. **HRMS-ESI**: calculated for $C_{12}H_{15}NOS_4$+H 238.1074, found 238.1098.



(*E*)-*N*-methoxy-*N*-methyl-3-(5-((*Z*)-8-(2-nitrophenylsulfonamido)oct-3-en-1-yl)furan-3-yl)acrylamide. To (5-(2-nitrophenylsulfonamido)pentyl)triphenyl-phosphonium iodide[19] (645 mg, 0.98 mmol) at -78 °C was added THF (7.0 mL). KHMDS (3.80 mL, 0.5 M in toluene) was added via syringe while keeping the reaction mixture with good stirring. A clear solution was obtained after 1h. Aldehyde **30** (197 mg, 0.83 mmol) was added via cannula (1.5 mL THF + 1.5 mL THF rinse). After 1h at -78 °C,

[19] Prepared from 5-amino-1-pentanol. (1) NsCl, Et_3N, DCM; (2) PPh_3, I_2, DCM; (3) PPh_3, CH_3CN.

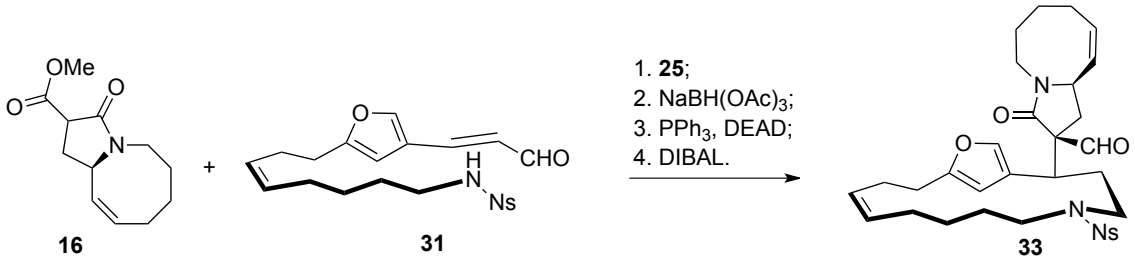
the reaction mixture was warmed to 0 °C and after 30 min was quenched with dropwise addition of HOAc until the color faded. The reaction mixture was concentrated and filtered through silica gel and washed with EtOAc. The filtrate was concentrated and purified by flash column chromatography with 30-50% EtOAc in hexanes to obtain the product (250 mg, 0.51 mmol, 64%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.11 (m, 1H), 7.83 (m, 1H), 7.72 (m, 2H), 7.55 (d, 1H), 7.50 (s, 1H), 6.67 (d, 1H), 6.24 (s, 1H), 5.32 (m, 3H), 3.73 (s, 3H), 3.27 (s, 3H), 3.06 (q, J = 6.5 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.32 (q, J = 7 Hz, 2H), 1.96 (q, J =7 Hz, 2H), 1.50 (quint, J = 7 Hz, 2H), 1.32 (quint, J = 7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.03, 157.42, 147.92, 143.04, 133.64, 133.54, 133.43, 132.65, 130.88, 130.09, 128.41, 125.17, 123.69, 114.77, 102.97, 61.69, 43.54, 32.34, 28.98, 27.9, 26.36, 26.19, 25.43. **IR** (film): 3366, 3009, 2939, 2863, 1655, 1610, 1542, 1418, 1363, 1170 cm^{-1}. **HRMS-ESI**: calculated for ($C_{23}H_{29}N_3O_7S$+H) 492.1804, found 492.1761.



31

2-nitro-*N*-((*Z*)-8-(4-((*E*)-3-oxoprop-1-en-1-yl)furan-2-yl)oct-5-en-1-yl)benzenesulfonamide (**31**). To a DCM (15 mL) solution of the Weinreb amide (113 mg, 0.23 mmol) at -78 °C was added DIBAL-H (0.40 mmol, 1M in toluene). Excess DIBAL-H was quenched with EtOAc, MeOH and H_2O was added later and the solution was warmed to room temperature. The prepicipitate was filtered through silica gel and washed with EtOAc. The filtrate was concentrated and purified by flash column chromatrography with 30% EtOAc in hexanes to obtain the product (83 mg, 0.19 mmol, 84%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.59 (d, J = 8.3 Hz, 1H), 8.12 (m, 1H), 7.85 (m, 1H), 7.73 (m, 2H),

7.63 (s, 1H), 7.35 (d, J = 16 Hz, 1H), 6.37 (dd, J = 15.6, 7.8 Hz, 1H), 6.22 (s, 1H), 5.34 (m, 2H), 5.26 (t, J = 6 Hz, 1H), 3.06 (q, J = 6.5 Hz, 2H), 2.66 (t, J = 7.3 Hz, 2H), 2.35 (q, J = 7 Hz, 2H), 1.98 (q, J = 7 Hz, 2H), 1.50 (quint, J = 7 Hz, 2H), 1.33 (quint, J= 7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 193.51, 158.32, 148.04, 144.2, 142.97, 133.66, 133.5, 132.74, 131.04, 130.32, 128.36, 128.15, 125.33, 123.51, 102.97, 43.66, 29.12, 27.89, 26.51, 26.3, 25.42. **IR** (film): 3349, 3008, 2935, 2860, 2734, 1673, 1634, 1596, 1541, 1415, 1363, 1343, 1167, 1125 cm^{-1}. **HRMS-ESI**: calculated for $C_{21}H_{25}N_2O_6S$ 433.1428, found 433.1434.

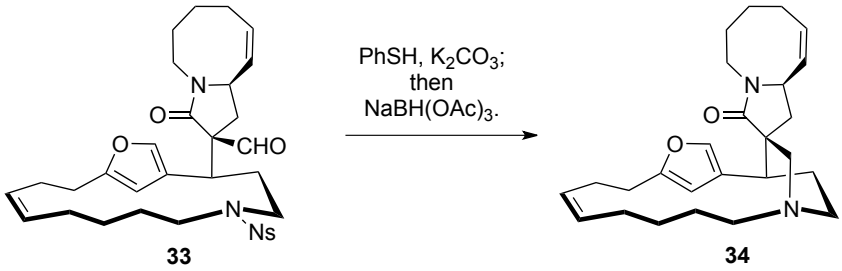


(2*R*,10a*R*,*Z*)-2-((*S*,*Z*)-5-((2-nitrophenyl)sulfonyl)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-trien-2-yl)-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carbaldehyde (**33**). A mixture of malonate **16** (64 mg, 0.29 mmol), aldehyde **31** (150 mg, 0.35 mmol) and catalyst **25** (12.3 mg, 0.038 mmol) in MeOH (0.25 mL) was stirred at rt for 48h and was concentrated. Flash column chromatography with 30-50% EtOAc in hexanes gave recovered aldehyde (27 mg) and Michael adduct (145 mg, 0.22 mmol, 77%) as a mixture of diastereoisomers.

The product was dissolved in DCM (2.5 mL) and stirred with $NaBH(OAc)_3$ (250 mg) overnight. The reaction mixture was filtered through silica gel and washed immediately with EtOAc to obtain the alcohol (150 mg).

The alcohol was stirred with PPh_3 (119 mg) in toluene (48 mL), DEAD (0.060 mL) was added dropwise via syringe over 10 min. After stirring another 10 min at rt, the reaction mixture was loaded on silica gel and flash column chromatography with 0-30-40-50% EtOAc in hexanes to afford the macrocycle as off-white foam (111 mg, 0.173 mmol, 78%, 2 steps).

To a toluene solution (1.0 mL) of macrocyclic malonate (45 mg, 0.070 mmol) at -78 °C was added DIBAL-H (0.15 mL, 1 M in toluene) dropwise. After 50 min, the reaction was quenched with EtOAc. MeOH and H_2O was added later and warmed to rt. After stirring 30 min, the precipitate was filtered through Celite and concentrated. Flash column chromatography with diethyl ether afforded the product (38 mg, 0.062 mmol, 89%). Separation of the diastereoisomers by preparative TLC with diethyl ether afforded the desired product **33** (13 mg, 0.021 mmol, 30%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.52 (s, 1H), 7.95 (m, 1H), 7.67 (m, 2H), 7.58 (m, 1H), 7.12 (s, 1H), 5.86 (s, 1H), 5.82 (app q, J = Hz, 1H), 5.34 (app q, J = Hz, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 4.08 (app q, J = Hz, 1H), 3.58 (q, J = Hz, 1H), 3.40 (ddd, J = Hz, 1H), 3.30 (dd, J = Hz, 2H), 3.20 (dd, J = Hz, 1H), 3.08 (m, 2H), 2.81 (ddd, J = Hz, 1H), 2.69 (ddd, J = Hz, 1H), 2.62 (ddd, J = Hz, 1H), 2.28 (m, 4H), 2.16 (m, 1H), 2.10 (m, 1H), 1.77-1.95 (m, 5H), 1.67 (m, 1H), 1.54 (m, 1H), 1.44 (m, 1H), 1.22 (m, 3H), 1.08 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 198.98, 169.73, 157.45, 148.15, 138.51, 133.34, 132.83, 131.58, 130.9, 130.62, 129.78, 129.45, 123.99, 123.09, 105.05, 64.29, 53.21, 48.21, 45.45, 41.32, 36.68, 29.67, 28.65, 27.6, 27.47, 26.85, 26.71, 25.99, 25.97, 25.73, 25.47. $[\alpha]^{23}_D = -61.6$ (*c* 0.81, $CHCl_3$). **IR** (film): 3055, 2986, 2934, 2868, 1730, 1676, 1546, 1422, 1374, 1265 cm^{-1}. **HRMS-ESI**: calculated for (M+H)+ $C_{32}H_{40}N_3O_7S$ 610.2581, found 610. 2590.



Lactam 34. A mixture of the aldehyde **33** (12.6 mg, 0.021 mmol), K_2CO_3 (20 mg, 0.14 mmol) and PhSH (19 mg, 0.17 mmol) in CH_3CN (0.20 mL) was stirred in a 50 °C oil bath for 30 min. the mixture was then cooled to rt and $NaBH(OAc)_3$ (33 mg, 0.16 mmol) was added and stirred for 2h. The reaction was quenched with Na_2CO_3 (aq) and extracted with DCM, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography with 10% MeOH in EtOAc obtained the product (7.3 mg, 0.018 mmol, 87%). For characterization data see compound **63** in Chapter 3.

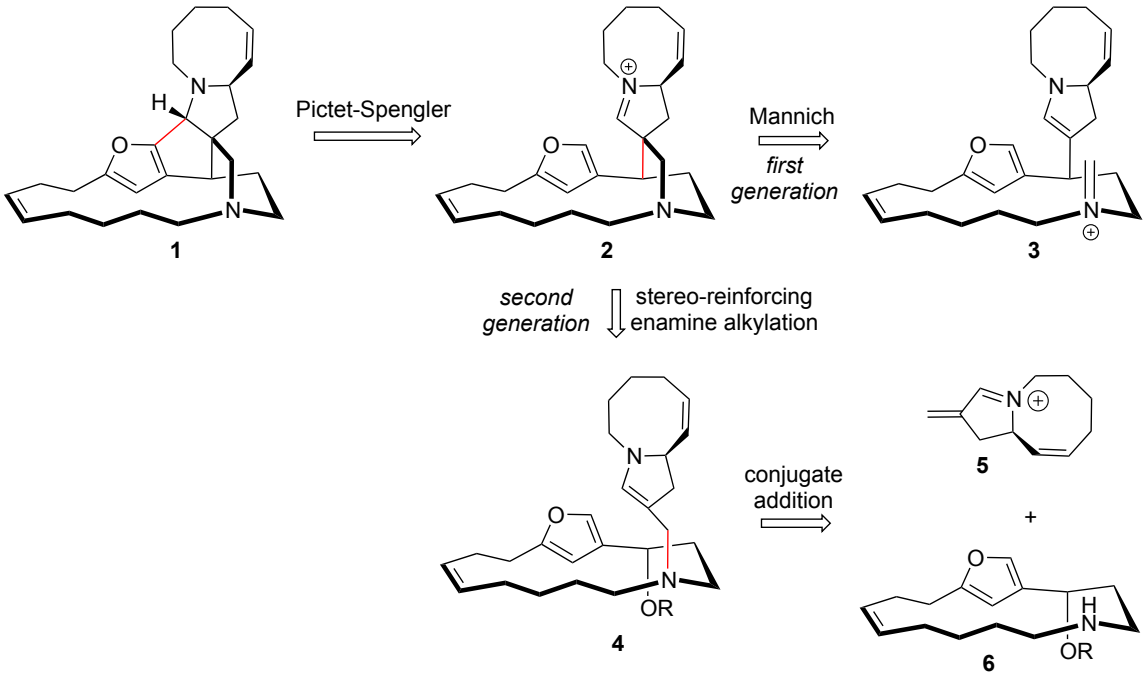
Chapter 3

Second Generation Route to the Total Synthesis of (−)-Nakadomarin A

I. Retrosynthetic Analysis

The second generation route to (−)-nakadomarin A (**1**) is presented in Scheme 3.1. Like the first generation route, it takes advantage of Pictet-Spengler reaction of iminium **2** to form (−)-nakadomarin A (**1**). However, iminium **2** would be generated by a stereo-reinforcing alkylation of enamine **4**,[1] instead of Mannich reaction of iminium **3**. Enamine **4** could be formed by a conjugate addition reaction of two fragments, macrocyclic amine **6** and α,β-unsaturated iminium **5**, both of similar size and complexity.[2]

Scheme 3.1. The second-generation retrosynthetic analysis of **1**.



[1] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

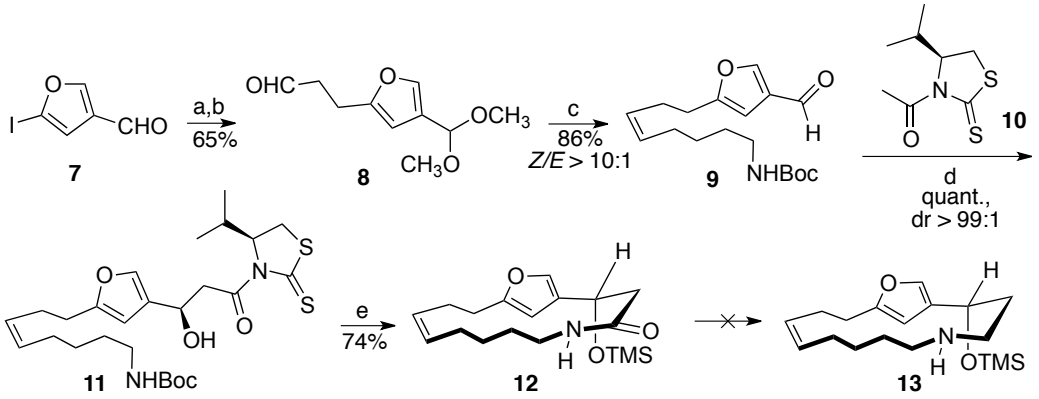
[2] Conjugate addition of nitrogen nucleophiles to unsaturated iminium: Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

II. Results and Discussion

1. Macrocyclic Amine Fragment

A macrolactamization approach was investigated first to prepare macrocyclic amine **6**.[3] Aldehyde **7** was protected as dimethyl acetal, and a Heck coupling reaction with allyl alcohol gave aldehyde **8**. Wittig olefination of **8** with ylide derived from $BocNH(CH_2)_5PPh_3I$ and acidic workup generated aldehyde **9**. An acetate aldol reaction of **9** with chiral auxiliary **10** gave alcohol **11** in high yield and diastereoselectivity.[4] The Boc group was removed with TFA and macrolactamization under basic conditions generated macrolactam **12**. Unfortunately, attempted reduction of the secondary amide to amine failed (Scheme 3.2).

Scheme 3.2. Macrolactamization route to macrocyclic amine fragment.



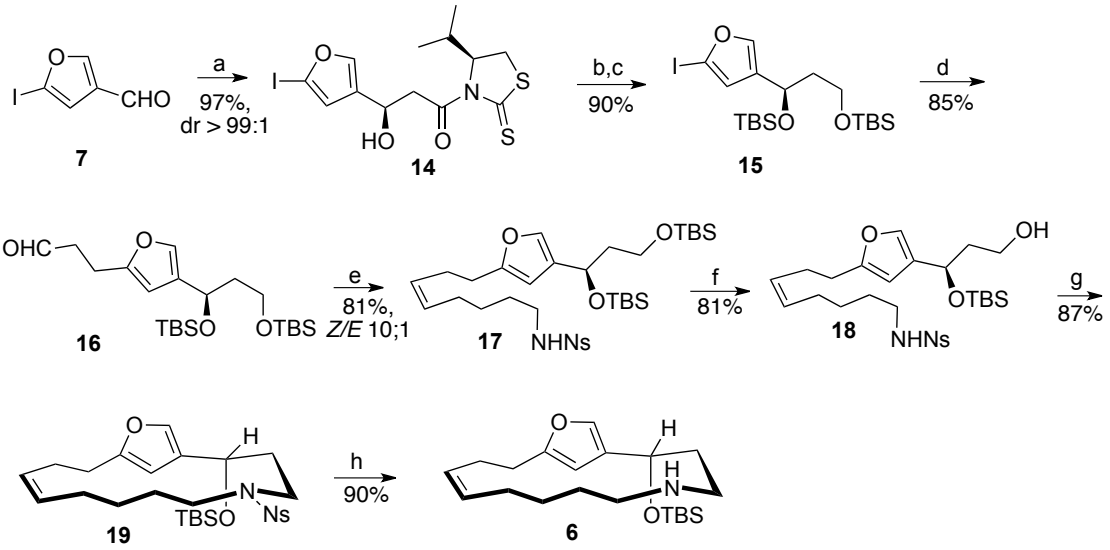
Reagents and conditions: (a) Amberlyst 15, $HC(OMe)_3$; (b) Bu_4NCl, $NaHCO_3$, allyl alcohol, $Pd(OAc)_2$ (5 mol%), 65% over 2 steps; (c) $BocNH(CH_2)_5PPh_3I$, KHMDS, then HCl (1 M), 86%, *Z/E* >15:1; (d) $Sn(OTf)_2$, *N*-ethylpiperidine, **10**, quant., single diastereoisomer; (e) TMSOTf, Et_3N then K_2CO_3 (aq), 74%.

[3] Macrolactam route was developed by Dr. Simone Bonazzi.

[4] Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.

On the other hand, acetate aldol reaction of **7** with **10** gave alcohol **14** in high yield and diastereoselectivity (Scheme 3.3).[5] Reductive cleavage of the auxiliary provided the diol, which was protected as bis-silyl ether **15**. Heck coupling of **15** with allyl alcohol gave aldehyde **16.** Wittig olefination with ylide derived from $NsNH(CH_2)_5PPh_3I$ gave compound **17**. Selective deprotection[6] of the primary alcohol with PPTS and Fukuyama-Mitsunobu alkylation[7] with PPh_3 and DEAD gave macrocycle **19** in good yield.[8] Structure determination of **19** was confirmed by X-ray crystallographic analysis (Figure 3.1). Removal of Ns group with PhSH gave macrocyclic amine **6**.

Scheme 3.3. Preparation of macrocyclic amine **6**.



Reagents and conditions: (a) $Sn(OTf)_2$, *N*-ethylpiperidine, **10**, DCM, 97%, dr > 99:1; (b) $LiBH_4$; (c) TBSOTf, 2,6-lutidine, > 90%, 2 steps; (d) Bu_4NBr, $NaHCO_3$, allyl alcohol, $Pd(OAc)_2$ (5 mol%), DMF, 85%; (e) $NsNH(CH_2)_5PPh_3I$, KHMDS, THF, 81%, *Z/E*~10:1; (f) PPTS, MeOH, 81%, one recycle; (g) PPh_3, DEAD, toluene (5 mM), rt, 87%; (h) PhSH, K_2CO_3, DMF, 90%.

[5] A combination of $TiCl_4/Et_3N$ also worked for this reaction and gave aldol product **14** in 85% yield with 30:1 dr.

[6] Crouch, R. D. *Tetrahedron*, **2013**, *69*, 2383–2417.

[7] Kan, T., Fukuyama, T. *Chem. Comm.*, **2004**, 353-359.

[8] An intermolecular double Fukuyama-Mitsunobu alkylation to generate **19** resulted in low yield (20%).

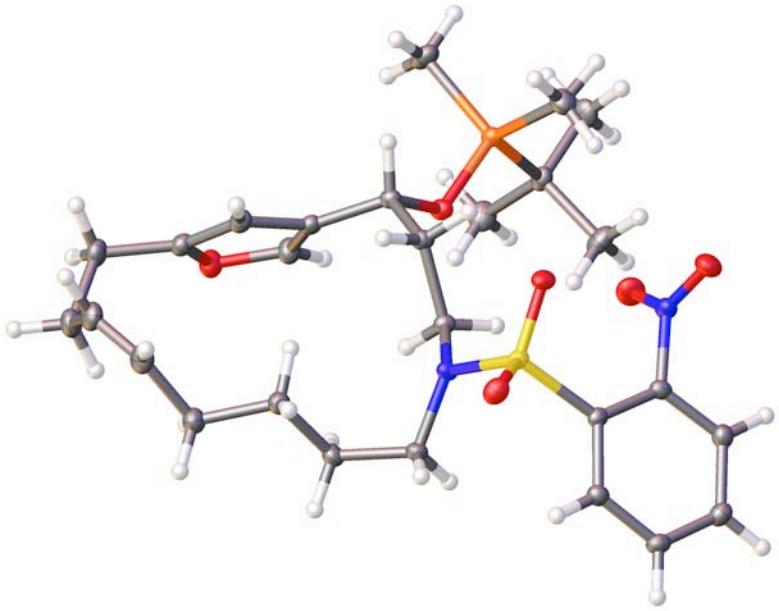


Figure 3.1. X-ray structure of macrocycle **19**.

2. Iminium Fragment[9]

The α,β-unsaturated iminium **5** was prepared from commercially available 4-pentyn-1-ol **20** (Scheme 3.4). Alkyne **20** was transformed into allylic alcohol **21** in three steps following a literature method.[10] Alcohol **21** was then converted to trichloroacetimidate **22** with trichloroacetonitrile and DBU, and a paladium catalyzed asymmetric catalytic Overman rearrangement[11] generated chiral allylic amide **23** in 93% yield and 94% ee. Amide **23** was hydrolyzed to give free amine **24**, and reductive amination with 5-hexenal provided diene **25**. Ring closing metathesis of **25** with Grubbs 2nd generation catalyst formed azocine **26**. Removal of silyl group, oxidation of the alcohol and α-methylenation

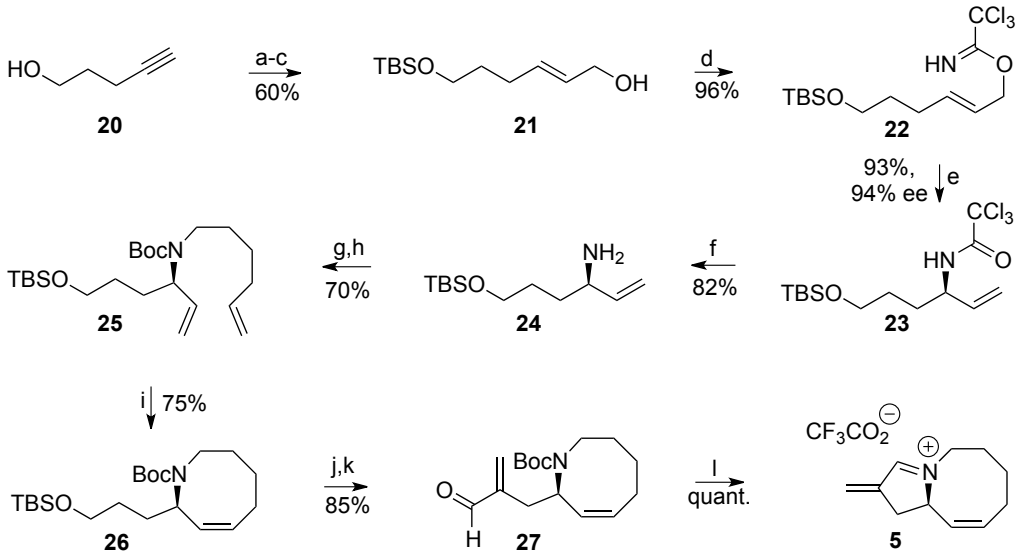
[9] Route was developed by Dr. Andrew Weiss and Dr. Simone Bonazzi.

[10] Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863-872.

[11] Anderson, C. E.; Overman, L. E.; Watson, M. P. *Org. Synth.* **2005**, *82*, 134.

of aldehyde gave enal **27**.[12] Removal of the Boc group with trifluoroacetic acid and *in situ* cyclization generated unsaturated iminium **5**.

Scheme 3.4. Preparation of unsaturated iminium **5**.



Reagents and conditions: (a) TBSCl, imidazole, 99%; (b) nBuLi, $(CH_2O)_n$, 79%; (c) Red-Al, 77%; (d) DBU, CH_3CN, 96%; (e) (*R*)-COP-Cl (5 mol%), K_2CO_3, 93%, 94% ee; (f) NaOH, EtOH, 82%; (g) 5-hexenal, MeOH, then $NaBH_4$; (h) Boc_2O, 70%, 2 steps; (i) Grubbs 2nd generation catatalyst, DCM, 35 °C 75%; (j) Dess-Martin periodinane; (k) pyrrolidine, 4-(dimethylamino)benzoic acid, $(CH_2O)_n$, 85%, 2 steps; (l) TFA, quant..

3. Fragment Coupling[13]

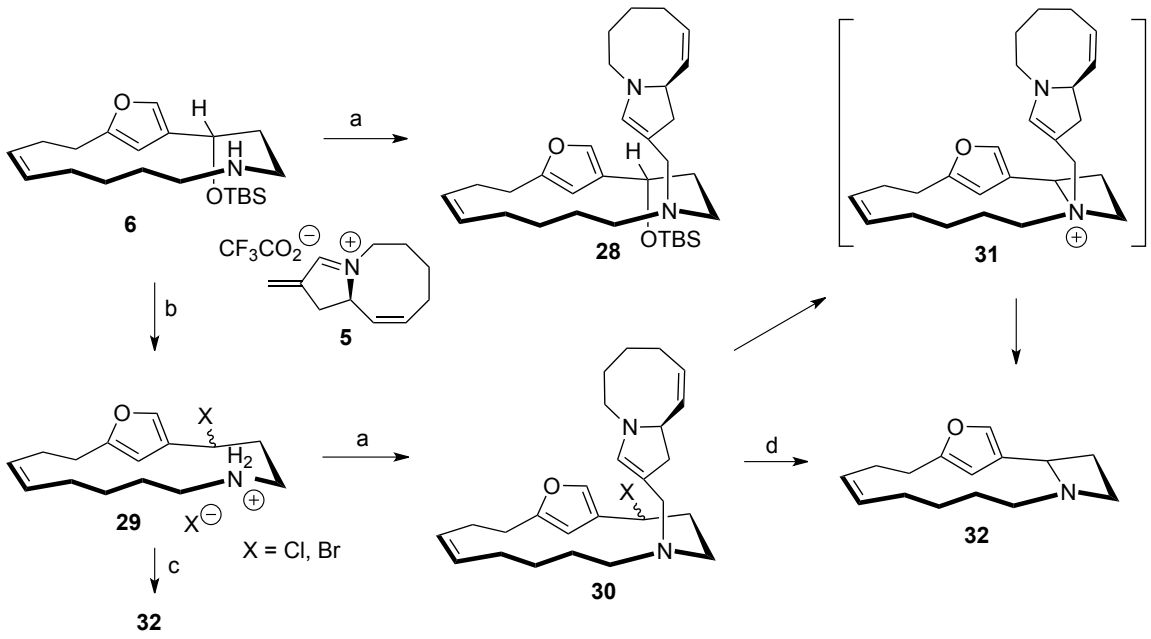
With both fragments in hand, conjugate addition of macrocyclic amine **6** to α,β-unsaturated iminium **5** was then investigated (Scheme 3.5). In the presense of 1,2,2,6,6-pentamethylpiperidine, the conjugate addition product enamine **28** was generated at low temperature, however was unstable to isolation, and only observed by the ^{1}H NMR spectroscopy. The presence of 1,2,2,6,6-pentamethylpiperidine was crucial for the first conjugate addition reaction. It quenched the trifluoroacetic acid generated from the conjugate addition, and prevented the decomposition of enamine **28**. No conjugate

[12] Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538-2541.

[13] This work was performed in collaboration with Dr. Simone Bonazzi.

addition was observed without base or with bases of weaker strength or smaller size (Et_3N, iPr_2NEt, etc.).

Scheme 3.5. Fragment coupling and attempted enamine alkylation reaction.



Reagents and conditions: (a) **5**, 1,2,2,6,6-pentamethylpiperidine, CD_3CN or CD_2Cl_2, -40 °C; (b) HOAc, HX (X = Cl, Br), quant.; (c) Et_3N, $CDCl_3$; (d) 0 °C (X = Cl) or -40 °C (X = Br).

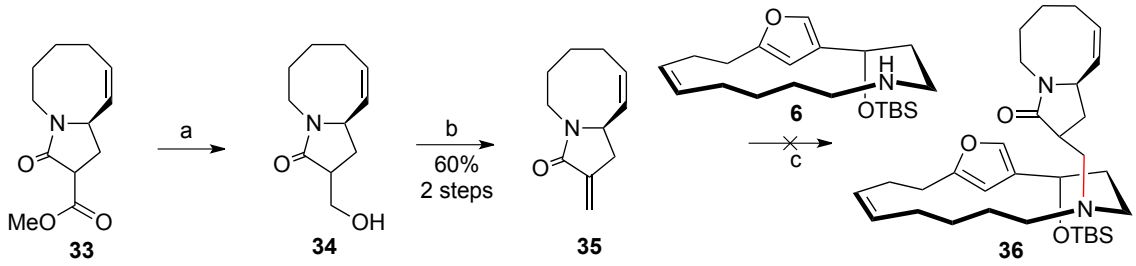
We then directed our efforts to installation of the leaving group for the enamine alkylation reaction. Macrocyclic compound **29** with a leaving group (X= Cl, Br) could be generated by treating **6** with HX (X= Cl, Br) in acetic acid. Under the same conditions as **28**, the conjugate addition product **30** was generated at low temperature. Unfortunately, when the solution was warmed up, no desired enamine alkylation product was observed. Instead, *N*-alkylation was more facile and formation of azetidine **32**, presumably via intermediate **31**, was observed. **32** was stable in solution, however, attempted isolation resulted in decomposition.

III. Modification of Bicyclic Iminium Fragment

To avoid formation of the azetidine **32**, it was necessary to either increase the nucleophilicity of enamine or decrease the nucleophilicity of macrocyclic nitrogen. Modification of the bicyclic iminium fragment was investigated first.

The first variant to be derived was unsaturated lactam **35**, since an amide enolate is predicated to be a better nucleophile than the corresponding enamine. The lactam was prepared from methyl malonate **33** in two steps. Reduction of ester **33** with $NaBH_4$ generated primary alcohol **34**, and subsequent dehydration with bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur **(**Martin's sulfurane)[14] provided unsaturated lactm **35**. Unfortunately, this lactam was a poor Michael acceptor, as attempted addition of macrocyclic amine **6** was not successful (Scheme 3.6).[15]

Scheme 3.6. Attempted addition of **6** to unsaturated lactam **35**.



Reagents and conditions: (a) $NaBH_4$, MeOH; (b) Martin's sulfurane, DCM, 60%, 2 steps; (c) **6**, heat or Lewis acid.

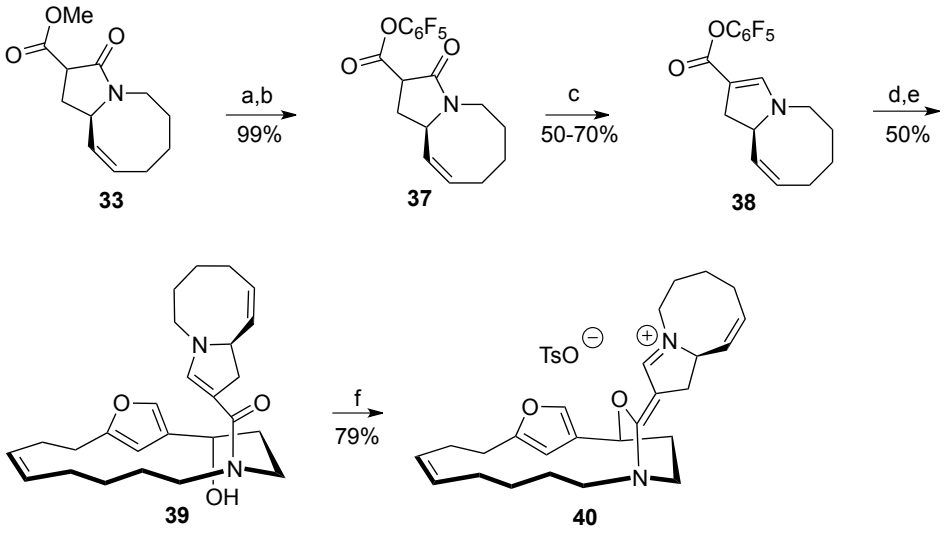
The second variant to our system was modification of the macrocyclic nitrogen, specifically, the incorporation of an electron-withdrawing carbonyl group adjacent to the nitrogen atom, such as that shown in **39**, to reduce its nucleophilicity (Scheme 3.7).

---

[14] Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.***1971**, *93*, 4327.

[15] The desired Michael adduct **36** was later prepared via reductive amination of the macrocyclic amine **6** with the aldehyde by Dr. Simone Bonazzi. Attempted alkylation also failed in this case.

Scheme 3.7. Attempted enamide alkylation.



Reagents and conditions: (a) LiOH, THF/H_2O; (b) $CF_3CO_2C_6F_5$, pyridine, DMF, 99%, 2 steps; (c) MeOTf, DCM; then $LiEt_3BH$, 50-70%; (d) DMAP, DMF, **6**; (e) TBAF, THF, 50%, 2 steps; (f) NaHMDS, TsCl, THF, 79%.

The modified enamine fragment **38** was prepared from **33** in three steps. The methyl ester of **33** was hydrolyzed and the resultant carboxylic acid was transformed into the activated ester **37**. In this case the pentafluorophenol ester[16] was chosen. Selective activation of the amide with MeOTf and reduction with Super-hydride® afforded enamide **38**.[17] Coupling of **38** with macrocyclic amine **6** afforded the amide and removal of the silyl protecting group generated alcohol **39**, a precursor for the cascade reaction. The alcohol of **39** was converted into a tosylate, and set the stage for nucleophilic substitution. Surprisingly, only the *O*-alkylation product **40** was obtained. The structure of **40** was elucidated by 1D and 2D NMR analysis and further confirmed by X-ray crystallographic analysis of a single crystal (Figure 3.2).

[16] Green, M.; Berman, J. *Tetrahedron Lett.* **1990**, *31*, 5851–5852.

[17] Tsay, S.; Robl, J. A.; Hwu, J. *J. Chem. Soc. Perkin. Trans. 1,* **1990**, 757.

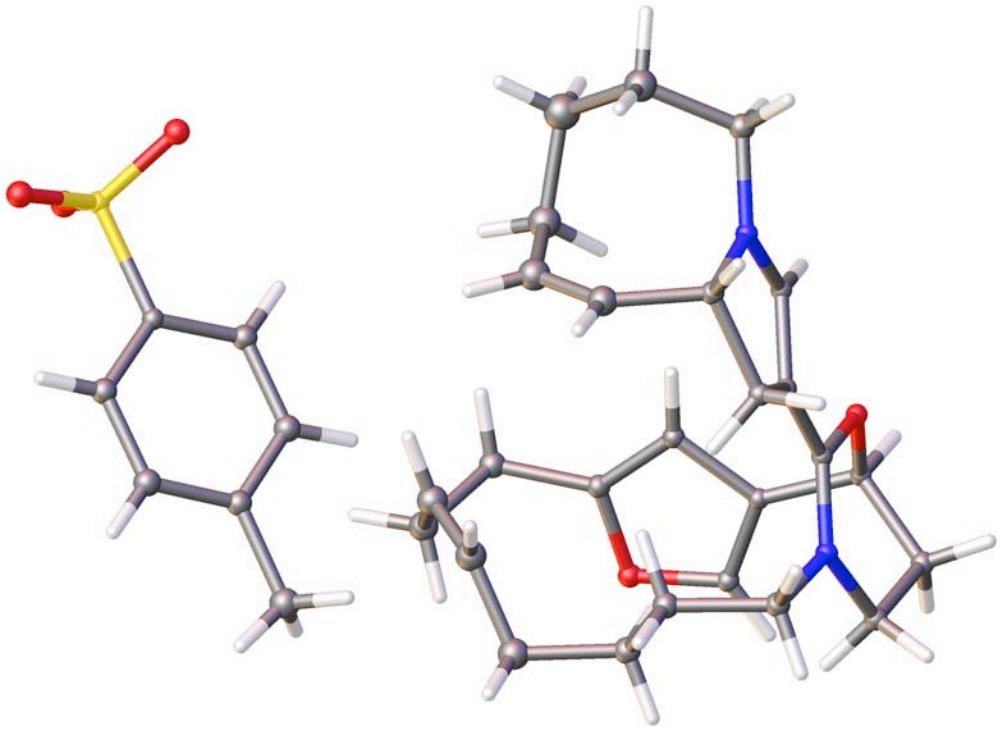


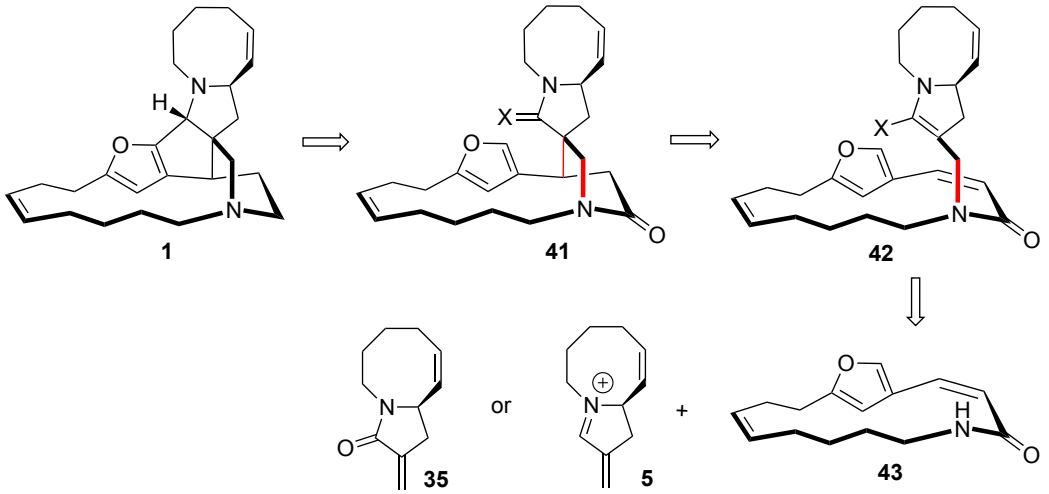
Figure 3.2. X-ray structure of compound **40**.

IV. Modification of the Macrocyclic Fragment[18]

Since modifications on the bicyclic iminium fragment did not lead to desired product, we decided to modify the macrocyclic fragment. Macrolactam **43** was envisioned as a viable fragment, and either lactam **35** or iminium **5** could act as a suitable Michael acceptor for **43**. Further, we also substituted the original enamine alkylation with a second conjugate addition (Scheme 3.8).

[18] Part of the results from this section has been published, see: Bonazzi, S.; Cheng, B.; Wzorek, J. S.; Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338–9341.

Scheme 3.8. Retrosynthetic analysis based on modification on the macrocyclic fragment.



1. Macrolactam Fragment[19]

Macrolactam fragment **43** was prepared from aldehyde **7**. The sequence commenced with *Z*-olefination of **7**, which afforded cis-unsaturated ester **44**.[20] Heck coupling of **44** with allyl alcohol under Jeffrey's condition gave aldehyde **45**. Wittig olefination of **45** generated cis olefin **46**.[21] The methyl ester of **46** was then hydrolyzed to the carboxylic acid and subsequent removal of the Boc group with TFA provided **47**. Macrolactamization of **47** with HBTU under dilute conditions afforded macrolactam **43**. Overall, the synthesis of **43** is 7 steps beginning from 3-furanaldehyde, and the fragment has been obtained on gram-scale (Scheme 3.9).

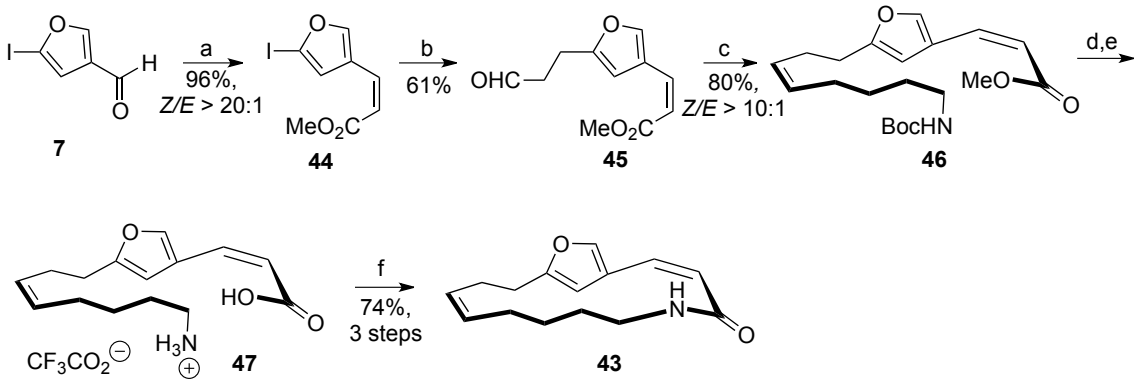
---

[19] The last 3 steps were developed by Dr. Simone Bonazzi.

[20] (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. (b) Sub-stoichiometric amount of 18-crown-6 could be used. Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teply, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150-9161.

[21] The reaction was run under dilute conditions (40 mM) to avoid isomerization of the cis-unsaturated ester, which was observed in reactions conducted at higher concentrations.

Scheme 3.9. Synthesis of macrolactam **43**.



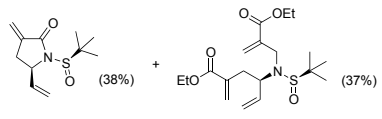
Reagents and conditions: (a) $(CF_3CH_2O)_2POCH_2CO_2Me$, KHMDS, 18-crown-6, 96%, *Z/E* > 20:1; (b) Bu_4NCl, $NaHCO_3$, $Pd(OAc)_2$, allyl alcohol, 61%; (c) $BocNH(CH_2)_5PPh_3I$, KHMDS, 80%; (d) NaOH, MeOH, H_2O; (e) TFA; (f) HBTU, Et_3N, CH_3CN, (2 mM), 74%, 3 steps.

2. Bicyclic Lactam Fragment

Bicyclic lactam fragment **35** was first synthesized from corresponding malonate **33**, however, an improved synthesis of this fragment was later developed as shown in Scheme 3.10. Condensation of acrolein with (*R*)-*tert*-butyl sulfinamide [22] gave unsaturated imine **49** in high yield. Allylation of **49** with commercially available ethyl 2-(bromomethyl)acrylate under Barbier conditions afforded homoallylic amine product **50**.[23] The chiral auxiliary of **50** was then removed with HCl in methanol, and basic work up with NaOH provided lactam **51** in good yield. Deprotonation of **51** and *in situ* quench

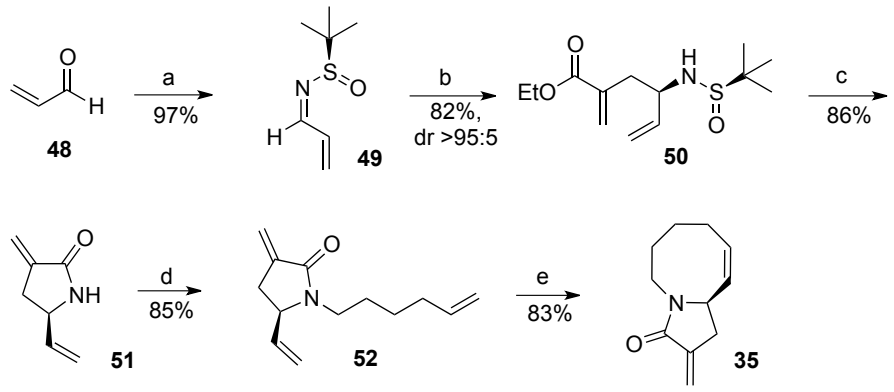
[22] (a) Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498; (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

[23] Shen, A.; Liu, M.; Jia, Z.-S.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5154. H_2O is critical for this reaction. In the absence of water, a mixture of two products, the lactam and the double allylation production, was obtained.



with 1-iodo-5-hexene afforded diene **52**.[24] Ring closing metathesis of **52** with Grubbs first generation catalyst gave desired bicyclic lactam **35**, 3.5 g of which has been obtained by this route.

Scheme 3.10. Improved synthesis of bicyclic lactam **35**.



Reagents and conditions: (a) $Ti(Oi\text{-}Pr)_4$, 97%; (b) ethyl 2-(bromomethyl)acrylate, Zn, LiCl, H_2O, DMF, 82%, dr > 95:5; (c) HCl, MeOH; then NaOH (s), 86%; (d) NaH, 1-iodo-5-hexene, 85%; (e) Grubbs first generation catalyst, DCM, (2 mM), 83%.

3. Fragment Coupling[25]

With fragments **35** and **43** prepared, fragment coupling was then investigated. After various screening and optimization efforts, it was found that slow addition of **35** to a solution of pre-activated **43** (TBSOTf, *i*Pr_2NEt) in dichloroethane afforded the desired fragment coupling product in 79% yield and 9:1 diastereoselectivity (Scheme 3.11).[26] Only two of the four possible product diastereomers were observed by ^{1}H NMR analysis

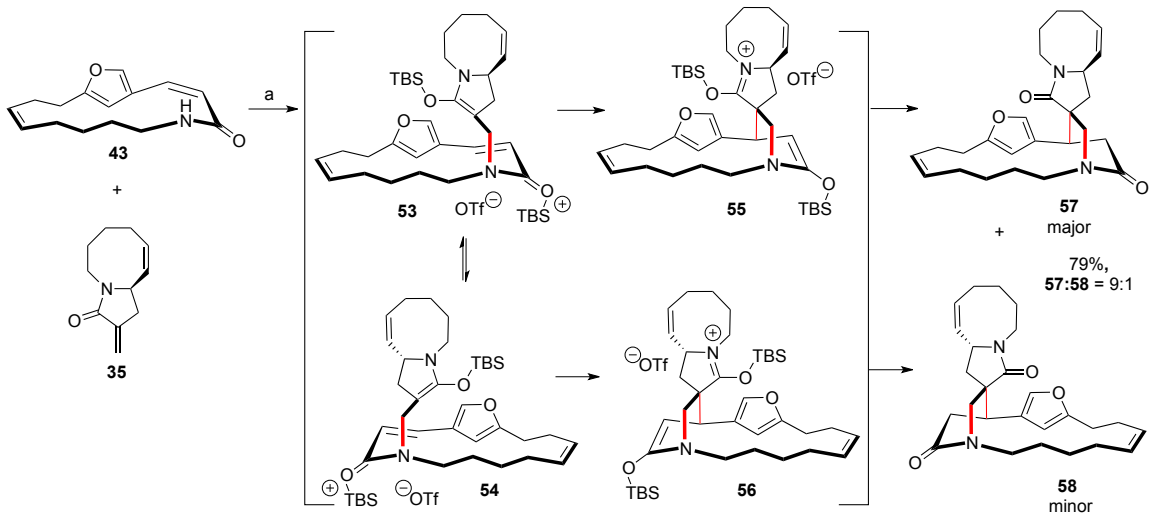
[24] The diene **52** could also be obtained from allylation product **50** directly (NaH or KHMDS, then 1-iodo-5-hexene), but in lower yield (40%).

[25] This fragment coupling reaction was developed by Dr. Simone Bonazzi.

[26] For double Michael addition reaction with TBSOTf/amine base, see (a) Takasu, K.; Nishida, N.; Ihara, M. *Tetrahedron Lett.* **2003**, *44*, 7429. (b) Takasu, K.; Nishida, N.; Tomimura, A.; Ihara, M. *J. Org. Chem.* **2005**, *70*, 3957. (c) Ihara, M.; Takino, Y.; Tomotake, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2287. (d) Ihara, M.; Kirihara, T.; Kawaguchi, A.; Tsuruta, M.; Fukumoto, K.; Kametan, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1719. (e) Takasu, K.; Nishida, N.; Ihara, M. *Synthesis* **2004**, 2222.

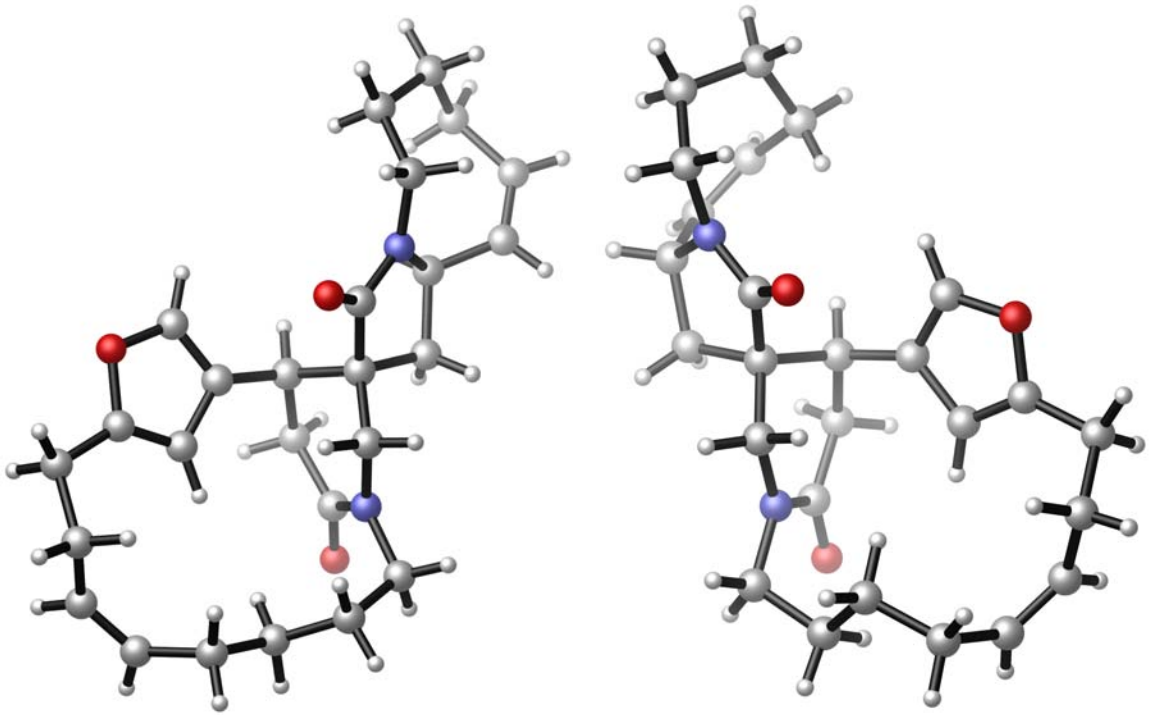
of the crude reaction mixture. The two diastereomers (**57** and **58**) were readily separable via silica gel flash column chromatography.

Scheme 3.11. Fragment coupling of **35** and **43**.



Reagents and conditions: (a) TBSOTf, iPr_2NEt, 1,2-dichloroethane; then slow addition of **35**, 79%, dr 9:1.

Both diastereomers **57** and **58** were characterized by 1D and 2D NMR spectroscopic analysis and their structures were further confirmed by X-ray crystallographic analysis (Figure 3.3). The structure of major product **57** has the desired stereochemistry corresponding to final target (−)-nakadomarin A (**1**), and addition of the achiral unsaturated macrolactam to the less hindered convex face of the bicyclic lactam (**53→55**) generated the quaternary center. The stereochemistry of the minor diastereomer **58** was quite surprising. It was unexpectedly derived from the addition of the opposite face of achiral unsaturated macrolactam to the more congested concave face of the bicyclic lactam (**54→56**).



57 **58**

Figure 3.3. X-ray structures of **57** and **58**.

The computed energies (B3LYP/6-31G*) of the four possible silicon-alkylated product diastereomers **59–62TMS** are provided in Figure 3.4.[27] The centro-symmetric trimethylsilyl moiety was used in place of the analogous TBS analogue to simplify the computations. As with any compromise, the relative energies of **59–62TMS** might under-represent the actual energy differences between **60TBS** and **61TBS**, as the TBS moiety is more sterically demanding than its TMS counterpart. Nevertheless, the energies of these structures substantiate that the most stable silylated structure is **59TMS**, an observation that is consistent with the structure of the major product diastereomer **57**. It is evident that both of the isolated product diastereomers (**57** and **58**) have their respective C═O dipoles disposed in an anti orientation, as predicted by the computations.

[27] Calculations were conducted by Dr. Joseph S. Wzorek.

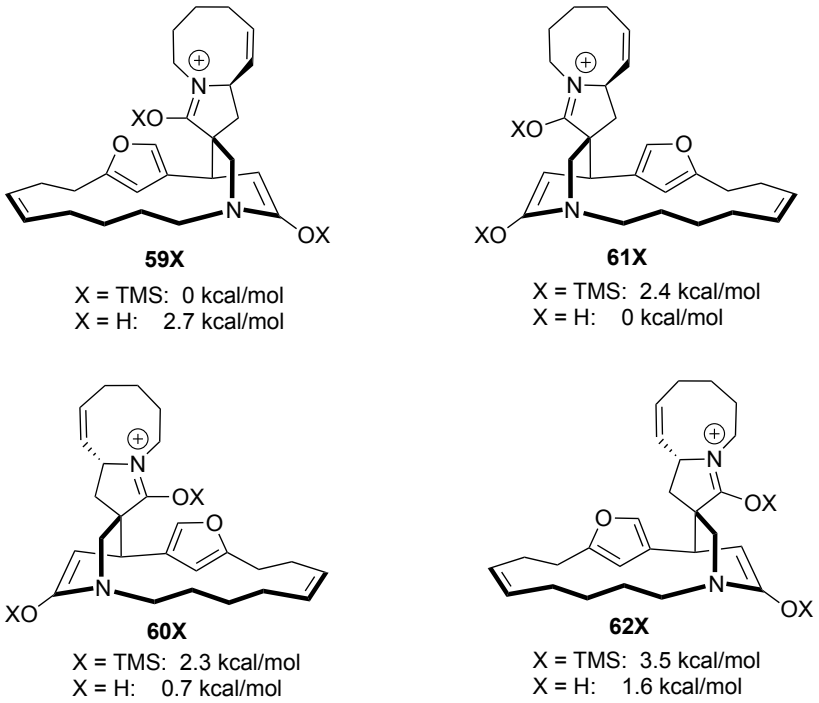


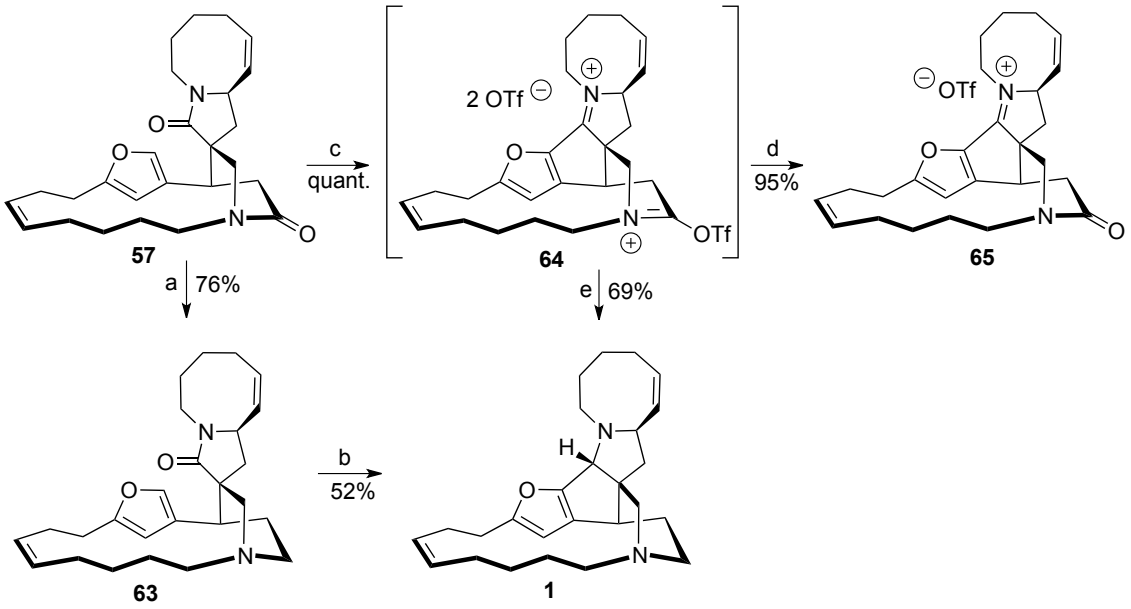
Figure 3.4. Computed energies (B3LYP/6-31G*) of silylated vs. protonated products.

Calculations for the protonated product diastereomers **59−62H** were also performed for comparison to probe the potential steric effects of the silicon substituent. The stability order of **59−62H** is quite different than that of **59−62TMS**. In this set of structures, **61H** is the most stable diastereomer. Hence, for structures **59−62H**, the computed product energies suggest that C−O dipole effects alone are not a major factor in determining the diastereomer stability, and possibly the kinetic selectivities. We thus conclude that the structure of the reaction promoter (TMSOTf or TBSOTf) seems to play a role in the observed reaction diastereoselectivity. It also appears that this reaction, first reported by Ihara, could well be a concerted rather than stepwise transformation.

4. Total synthesis of (−)-nakadomarin A[28]

With an efficient route to pentacyclic compound **57** established, completion of the total synthesis of our targeted natural product (−)-nakadomarin A (**1**) was then investigated (Scheme 3.12).

Scheme 3.12. Total synthesis of (−)-nakadomarin A (**1**).



Reagents and conditions: (a) Me_3OBF_4, 4 Å MS, DCM, rt, 2 h, then $NaBH_4$, MeOH, 0 °C to rt, 76%; (b) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, rt, 30 min, then $NaBH_3CN$, MeOH, rt, 52%; (c) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, rt, 2 h; (d) Na_2CO_3 (aq); e) Red-Al, −78 to 60 °C, 3 h, 69%.

When compound **57** was treated with electrophiles such as Meerwein's salt (Me_3OBF_4), selective reactivity at the less hindered δ-lactam was observed. Treatment of the activated amide intermediate with $NaBH_4$ in methanol gave known lactam **63**.[29] To complete the synthesis, treatment of lactam **63** using modified conditions similar to those reported by Dixon and co-workers (Tf_2O and 2,6-di-tert-butyl-4-methylpyridine),

[28] The two-step procedure was developed by Dr. Simone Bonazzi.

[29] Jakubec, P.; Kyle, A.F; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011***, 52,* 6094-6097. Also compound **34** in Chapter 2.

facilitated the activation of the γ-lactam, and cyclized with the furan to afford iminium intermediate. Subsequent reduction using $NaBH_3CN$ afforded (−)-nakadomarin A (**1**). The spectra data for synthetic (−)-nakadomarin A matched with the reported literature data (^1H and ^{13}C NMR, HRMS, IR, and optical rotation).[30] A single crystal of the hydrochloride salt of (−)-nakadomarin A was obtained by slow diffusion of diethyl ether vapor to its 2-propanol solution (mp > 260 °C), and X-ray crystallographic analysis confirmed the structure (Figure 3.5).

A one-pot procedure to convert **57** to (−)-nakadomarin A was later developed. When **57** was activated with the stronger electrophile Tf_2O, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine,[31] a complete and clean cyclization reaction took place rapidly as observed by ^1H NMR. The disappearance of the furan 2-H peak (δ 7 ppm) indicated cyclization of the furan with the activated amide. Aqueous work-up of the reaction mixture with Na_2CO_3 (aq) gave iminium **65**. Alternatively, addition of a reducing reagent to the reaction mixture would afford (−)-nakadomarin A directly. After screening of a variety of reducing agents, Red-Al was found to give the best results and (−)-nakadomarin A (**1**) was obtained in 70% yield from **57**.

In conclusion, total synthesis of (−)-nakadomarin A was completed in 9 steps (longest linear sequence, 14 steps in total) from 3-furaldehyde with 10% overall yield. More than 500 mg (−)-nakadomarin A has been prepared following this route.

---

[30] See the experiment section for the full characterization of synthetic (−)-nakadomarin A, and Appendix II for spectra comparison with the literature data.

[31] In the absence of base, the reaction was very slow and the reaction was not clean.

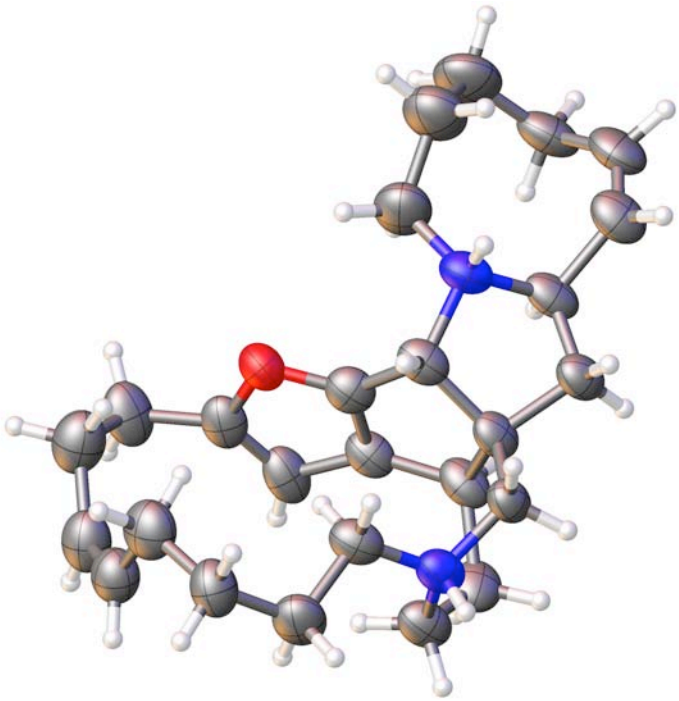


Figure 3.5. X-ray structure of (–)-nakadomarin A•2HCl.

V. Fragment Coupling with Iminium

With the success of bicyclic lactam fragment **35** in the cascade reaction leading to (–)-nakadomarin A, iminium fragment **5** was also investigated as a means to access the natural product. Iminium **5** was originally prepared in 12 steps, however, a more step-economical synthesis was developed, in a way similar to that of bicyclic lactam **35**.

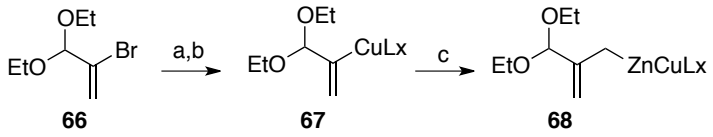
1. Iminium Fragment

The allylation reagent **68** was prepared in accordance with literature precedent from commercially available 2-bromopropenal diethylacetal **66**.[32] A lithium-halogen exchange reaction of **66** with *n*-BuLi, followed by transmetalation with CuBr•SMe_2 generated

[32] Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291.

vinyl cuprate **67**. Homologation of vinyl cuprate with zinc carbenoid $Zn(CH_2I)_2$[33] generated allylzinc reagent **68** (Scheme 3.13).

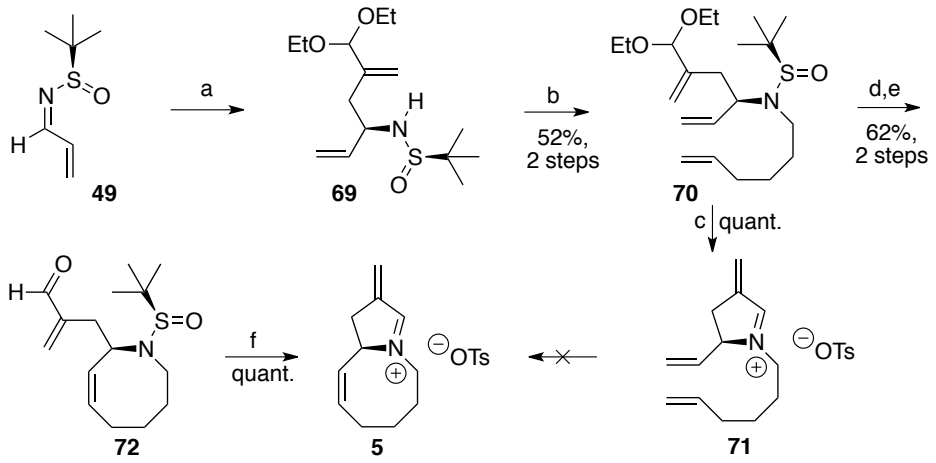
Scheme 3.13. Preparation of allylzinc reagent.



Reagents and conditions: (a) *n*-BuLi; (b) $CuBr•SMe_2$; (c) $Zn(CH_2I)_2$.

Treatment of the *in situ* derived allylzinc **68** with imine **49** generated homoallylic amine derivative **69** (Scheme 3.14).[34] *N*-alkylation furnished diene **70**, and treatment with TsOH gave iminium **71**. Attempted ring closing metathesis of iminium **71** only resulted

Scheme 3.14. Synthesis of iminium **5**.



Reagents and conditions: (a) **68**; (b) NaH, 1-iodo-5-hexene, DMF, 52%, 2 steps, dr > 10:1; (c) TsOH, MeOH, quant.; (d) oxalic acid (aq), THF, 94%; (e) Hoveyda-Grubbs 2nd generation catalyst (20 mol%), toluene, 110 °C, 66%; (f) TsOH, MeOH, quant..

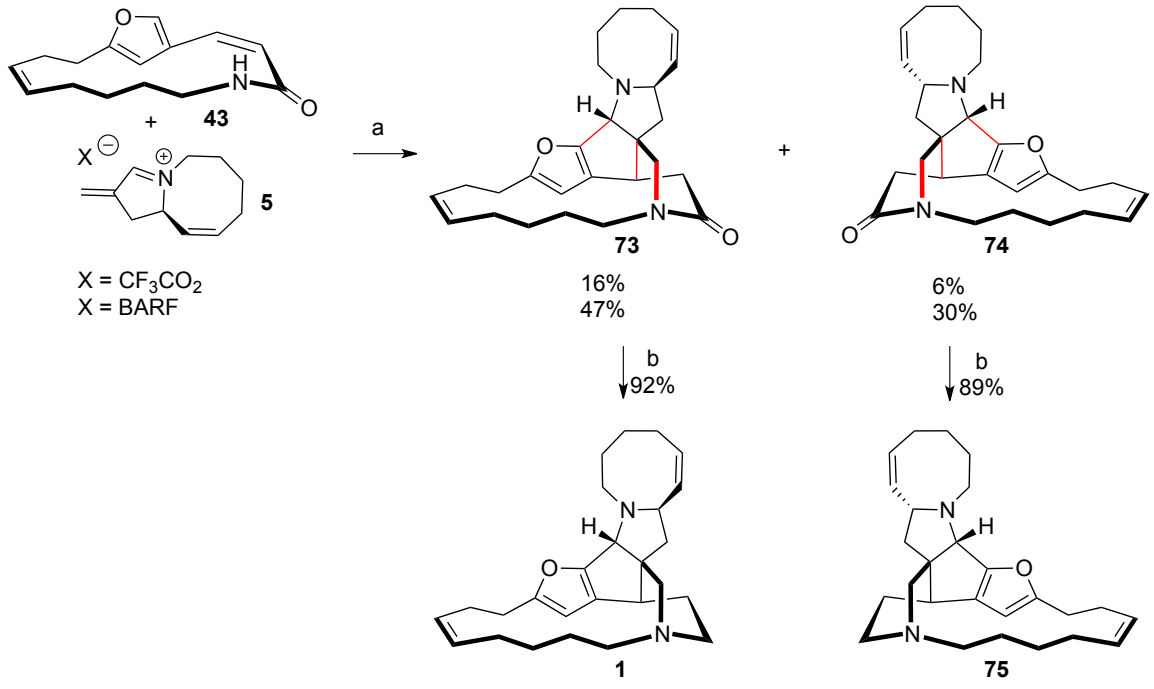
[33] Sidduri, A. R.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694. Generated from CH_2I_2 and Et_2Zn in a separated flask and then transferred into the vinyl cuprate solution.

[34] In the absence of other electrophiles, the allylzinc will further react with $Zn(CH_2I)_2$ to give the double methylene insertion product. Marek, I. *Tetrahedron* **2002**, *58*, 9463.

in decomposition. On the other hand, hydrolysis of acetal **70** with oxalic acid[35] provided the corresponding unsaturated aldehyde. Subsequent ring closing metathesis with the second generation Grubbs-Hoveyda catalyst afforded desired product **72**. The targeted iminium **5** was obtained by treating compound **72** with TsOH in methanol.

Slow addition of iminium **5** to a solution of pre-activated macrolactam **43** provided the fragment coupling products **73** and **74**.[36] The reaction is highly dependent on the counteranion of iminium **5**. BARF gave good yield, but poor selectivity, while TFA gave enhanced selectivity, but with lower yield. The reaction with tosylate anion is under investigation. Reduction of **73** with $LiAlH_4$ afforded (–)-nakadomarin A. Reduction of **74** gave *epi*-nakadomarin **75**, which is the same as that obtained from **58** (Scheme 3.15).

Sheme 3.15. Cascade reaction with iminium **5**.

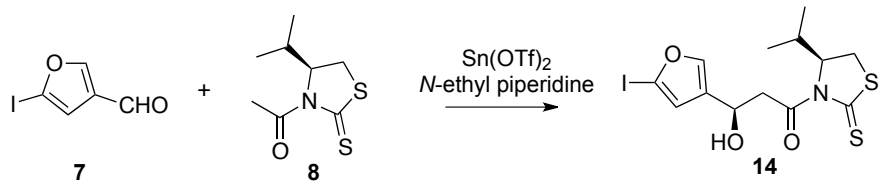


Reagents and conditions: (a) TBSOTf, *N*-methyl morpholine, 1,2-dichloroethane, then **5,** 50 °C; (b) $LiAlH_4$, THF.

[35] Caine, D.; Venkataramu, S. D.; Kois, A. *J. Org. Chem.* **1992**, *57*, 2960-2963.

[36] Experiments were performed by Dr. Simone Bonazzi.

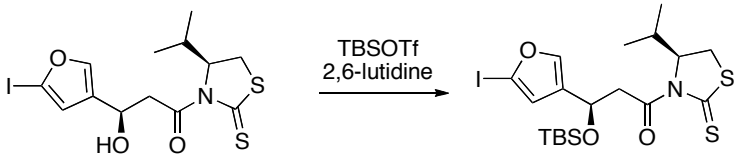
VI. Experimental Section



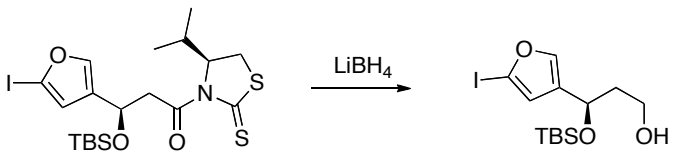
(*R*)-3-hydroxy-3-(5-iodofuran-3-yl)-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)propan-1-one (**14**). *N*-ethylpiperidine (1.75 mL, 12.7 mmol) was added to a suspension of $Sn(OTf)_2$ (5.25 g, 12.6 mmol) in DCM (20 mL) at –45 °C with a dry ice/acetone cooling bath. The mixture was stirred for 15 min, then a solution of 3-acetyl-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione[37] (2.24 g, 11.0 mmol) in DCM (5 mL) was added via syringe, with a DCM (5 mL) rinse. The mixture was stirred for 3 h at –30 to –20 °C to form the tin(II) enolate, then cooled to –78 °C. 5-Iodo-3-furancarboxaldehyde (1.87 g, 8.42 mmol) in DCM (5 mL) was added via syringe, with a DCM (3 mL) rinse. The reaction mixture was stirred for 4 h, quenched with pH=7 phosphate buffer solution, and extracted with DCM. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography with 0–30% EtOAc in hexanes to afford the acetate aldol product (3.46 g, 8.14 mmol, 97%) as a single diastereoisomer. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.47 (s, 1H), 6.54 (s, 1H), 5.11 (m, 2H), 3.72 (m, 1H), 3.48 (m, 2H), 3.36 (br s, 1H), 3.01 (d, *J* = 11.7 Hz, 1H), 2.31 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 202.9, 171.8, 143.9, 130.4, 118.9, 88.9, 71.2, 62.8, 45.5, 30.64, 30.59, 18.9, 17.7. **$[\alpha]^{23}_D$** = 222.3 (*c* 0.98, $CHCl_3$). **IR** ($CDCl_3$ film): 3447, 3132,

[37] Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.

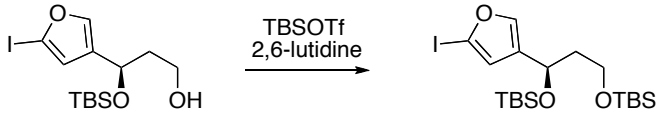
2963, 2874, 1694, 1472 cm^{-1}. **HRMS-ESI**: calculated for $[C_{13}H_{16}INO_3S_2+Na]^+$ 447.9508; found 447.9506.



To a solution of acetate aldol product (3.46 g, 8.14 mmol) in DCM (50 mL) at –78 °C was added 2,6-lutidine (2.0 mL, 17 mmol) and TBSOTf (3.0 mL, 13 mmol) sequentially. The mixture was stirred for 1.5 h and TLC (20% EtOAc in hexanes) showed completion of the reaction. The mixture was warmed to 0 °C, quenched with pH=7 phosphate buffer solution, extracted with DCM and dried over Na_2SO_4. Flash column chromatography with 0–20% EtOAc in hexanes provided the silyl ether as a light yellow solid (4.20 g, 7.78 mmol, 95%). The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **Mp**: 69–71 °C. $\mathbf{[\alpha]^{23}_D}$ = 227.3 (*c* 1.07, $CHCl_3$). **IR** ($CDCl_3$ film): 2956, 2855, 1694, 1470 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.43 (s, 1H), 6.54 (s, 1H), 5.25 (dd, *J* = 8.5, 4.1 Hz, 1H), 5.04 (ddd, *J* = 7.3, 6.1, 0.9 Hz, 1H), 3.82 (dd, *J* = 17.0, 8.5 Hz, 1H), 3.48 (dd, *J* = 11.4, 7.9 Hz, 1H), 3.28 (dd, *J* = 16.7, 4.1 Hz, 1H), 3.03 (dd, *J* = 11.4, 1.2 Hz, 1H), 2.34 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), -0.05 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 202.8, 170.8, 143.9, 131.9, 119.3, 88.4, 71.6, 64.1, 47.5, 30.9, 30.7, 25.7, 19.1, 18.0, 17.8, -4.6, -5.1. **HRMS-ESI**: calculated for $[C_{19}H_{30}INO_3S_2Si+Na]^+$ 562.0373; found 562.0346.

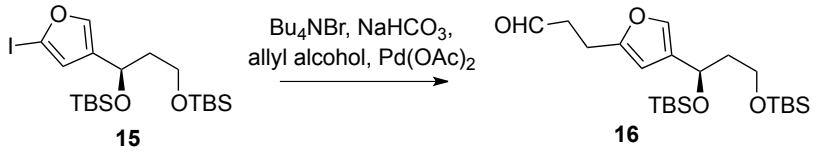


A solution of $LiBH_4$ (5 ml, 2.0 M solution in THF, 10 mmol) was added to a stirred solution of TBS ether (1.38 g, 2.56 mmol) in DCM/MeOH (11 mL, 10:1) at 0 °C. The reaction was quenched with saturated $NaHCO_3$ after 1 h. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4. The solution was concentrated and the crude product was used without further purification. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. $\mathbf{[\alpha]^{23}_D}$ = 51.1 (*c* 1.01, $CHCl_3$). **IR** (neat): 3364, 3134, 2953, 2885, 2858, 1472 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H), 6.47 (s, 1H), 4.91 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.75 (ddd, *J* = 11.2, 7.8, 4.4 Hz, 1H), 3.65 (m, 1H), 2.14 (bs, 1H), 1.95-1.81 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), -0.04 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 143.8, 132.1, 119.0, 88.4, 66.5, 59.7, 40.7, 25.7, 18.0, -4.8, -5.2. **HRMS-ESI**: calculated for $[C_{13}H_{23}IO_3Si+Na]^+$ 405.0353; found 405.0354.

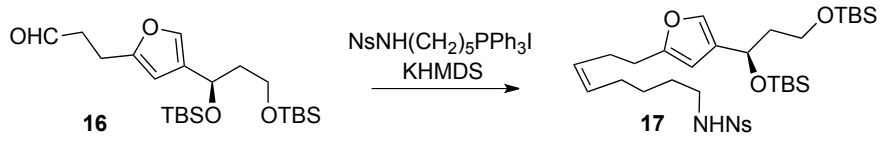


(*R*)-5-(5-iodofuran-3-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**15**). To a solution of the above product in DCM (10 mL) at 0 °C was added 2,6-lutidine (1.0 mL) and TBSOTf (0.78 mL). The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was loaded onto a silica gel column and eluted with 0- 10% EtOAc in hexanes to give the TBS ether (1.25 g, 98% over 2 steps). The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.37 (s, 1H), 6.50 (s, 1H), 4.81 (dd, *J* = 7.3, 5.4 Hz, 1H), 3.70 (ddd, *J* = 10.3, 6.8, 5.9 Hz, 1H), 3.57 (app dt, *J* = 10.2, 5.9 Hz, 1H), 1.88 (m, 1H),), 1.75 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H),

0.03 (s, 3H), -0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7, 133.0, 119.3, 87.9, 64.0, 59.2, 42.5, 25.9, 25.8, 18.2, 18.1, -4.7, -5.1, -5.31, -5.33. **$[\alpha]^{23}_D$** = 22.2 (*c* 1.26, $CHCl_3$). **IR** (neat): 3135, 2929, 2858, 1472 cm^{-1}.



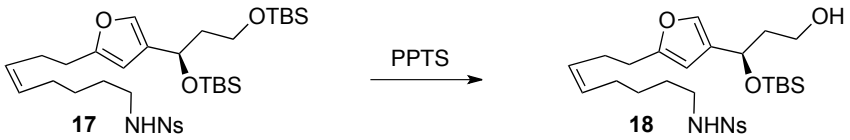
(*R*)-3-(4-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-5-yl)furan-2-yl)propanal (**16**). A mixture of iodide **15** (6.39 g, 12.9 mmol), Bu_4NBr (5.51 g, 17.1 mmol), $NaHCO_3$ (3.30 g, 39.3 mmol), $Pd(OAc)_2$ (145 mg, 0.646 mmol, 5.0 mol%), allylic alcohol (9.0 mL, 127 mmol) in DMF (20 mL) was stirred in a 40 °C oil bath for 48 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether and filtered through Celite. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography with 2-4% EtOAc in hexanes to give aldehyde **16** (4.65 g, 10.9 mmol, 85%) as light yellow oil. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.82 (1H), 7.14 (s, 1H), 5.98 (s, 1H), 4.76 (dd, *J* = 7.5, 5.5 Hz, 1H), 3.70 (dt, *J* = 10.3, 6.5 Hz, 1H), 3.58 (dt, *J* = 10.3, 6.3 Hz, 1H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 1.88 (m, 1H),), 1.76 (m, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), -0.06 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 201.2, 154.3, 137.5, 130.7, 105.1, 64.6, 59.7, 42.7, 42.1, 26.1, 26.0, 21.1, 18.5, 18.4, -4.4, -4.8, -5.1, -5.1. **$[\alpha]^{23}_D$** = 27.3 (*c* 1.12, $CHCl_3$). **IR** (neat): 3113, 2956, 2929, 2885, 2856, 2719, 1731, 1472 cm^{-1}. **HRMS-ESI**: calculated for $[C_{22}H_{42}O_4Si_2+Na]^+$ 449.2514; found 449.2505.



(*R*,*Z*)-2-nitro-*N*-(8-(4-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-5-yl)furan-2-yl)oct-5-en-1-yl)benzenesulfonamide (**17**). A solution of KHMDS (0.68 mL, 0.9 M solution in THF, 0.61 mmol) was added to a suspension of 5-(2-nitrobenzenesulfonylamido)pentyl triphenylphosphonium iodide[38] (203 mg, 0.307 mmol) in THF (2 mL) at –78 °C. The mixture was stirred for 30 min, until a clear dark red solution was obtained. The aldehyde (103 mg, 0.242 mmol) in THF (0.5 mL) was added via cannula, followed by a THF (0.5 mL) rinse. The mixture was stirred for 1 h at –78 °C and then 30 min at 0 °C. A deep purple solution was obtained. The reaction was quenched by the dropwise addition of acetic acid until the color faded. The mixture was diluted with EtOAc, filtered through silica gel, and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash column chromatography with 0–20% EtOAc in hexanes to give the product (134 mg, 0.197 mmol, 81%), ^{1}H NMR analysis showed ~ 10:1 *Z/E* ratio. The minor isomer was further removed by silica gel column impregnated with $AgNO_3$. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.14-7.70 (m, 4H), 7.13 (s, 1H), 5.94 (s, 1H), 5.38-5.24 (m, 3H), 4.76 (dd, *J* = 7.3, 5.3 Hz, 1H), 3.70 (dt, *J* = 10.0, 6.7 Hz, 1H), 3.59 (dt, *J* = 10.3, 6.3 Hz, 1H), 3.10 (q, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.28 (q, *J* = 7.3 Hz, 2H), 1.98 (, *J* = 7.3 Hz, 2H), 1.90 (m, 1H), 1.77 (m, 1H), 1.52 (m, 2H), 1.35 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), -0.06 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 155.8,

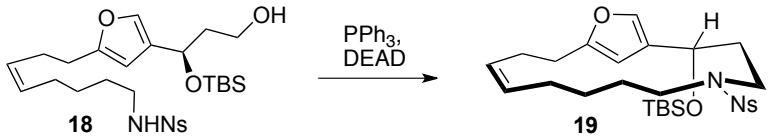
[38] Prepared in 3 steps from 5-amino-1-pentanol: a, NsCl, Et_3N, DMAP; b, PPh_3, I_2, imidazole; c, PPh_3.

148.1, 136.8, 133.8, 133.5, 132.7, 131.1, 130.3, 129.7, 129.0, 125.3, 104.4, 64.5, 59.5, 43.7, 42.5, 29.1, 28.2, 26.5, 26.4, 25.9, 25.8, 25.7, 18.22, 18.18, -4.6, -5.0, -5.3. $[\alpha]^{23}_{D}$ = 18.0 (*c* 1.47, $CHCl_3$). **IR** (neat): 3353, 3098, 2954, 2928, 2886, 2857, 1594, 1543, 1472, 1361, 1256, 1170, 1094 cm^{-1}. **HRMS-ESI**: calculated for $[C_{33}H_{56}N_2O_7SSi_2+Na]^+$ 703.3239; found 703.3233.



(*R*,*Z*)-*N*-(8-(4-(1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxypropyl)furan-2-yl)oct-5-en-1-yl)-2-nitrobenzenesulfonamide (**18**). A solution of TBS ether (235 mg, 0.346 mmol) and PPTS (8.9 mg, 0.0355 mmol, 10 mol%) in ethanol (3.5 mL) was stirred at room temperature for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography with 0–100% EtOAc in hexanes. Desired mono-deprotected product (120 mg) was obtained. Recovered starting material (74 mg) was treated with PPTS (2.4 mg) in ethanol (1 mL) for 5 h and worked up as above. Starting material (15 mg, 6%) and additional product (38 mg) were obtained, resulting in a combined yield of 81% (158 mg, 0.279 mmol). The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.14-7.70 (m, 4H), 7.17 (s, 1H), 5.93 (s, 1H), 5.37-5.25 (m, 3H), 4.90 (dd, *J* = 6.4, 4.6 Hz, 1H), 3.77 (dd, *J* = 11.0, 7.8, 4.1 Hz, 1H), 3.69 (ddd, *J* = 10.8, 6.0, 4.7 Hz, 1H), 3.08 (q, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.30 (q, *J* = 7.3 Hz, 2H), 1.97 (q, *J* = 7.3 Hz, 2H), 1.94 (m, 2H), 1.51 (m, 2H), 1.34 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), -0.05 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 156.1,

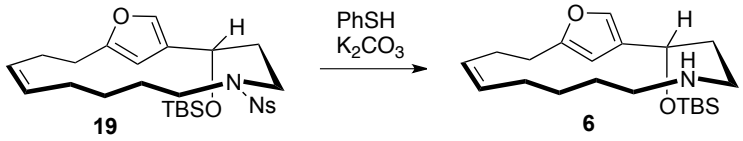
148.1, 137.0, 133.7, 133.5, 132.7, 131.0, 129.8, 129.4, 128.9, 125.3, 104.3, 67.5, 60.2, 43.7, 40.6, 29.1, 28.1, 26.5, 26.3, 25.7, 25.6, 18.0, -4.7, -5.2. $[\alpha]^{23}_{D}$ = 27.3 (*c* 0.40, $CHCl_3$). **IR** (neat): 3521, 3354, 3098, 3007, 2931, 2857, 1594, 1540, 1538, 1472, 1361, 1256, 1170 cm^{-1}. **HRMS-ESI**: calculated for $[C_{27}H_{42}N_2O_7SSi+Na]^+$ 589.2374; found 589.2365.



18 **19**

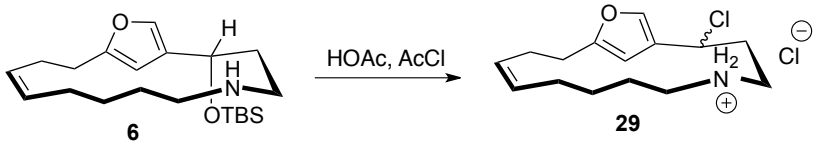
(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-5-((2-nitrophenyl)sulfonyl)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-triene (**19**). To a stirred solution of alcohol (210 mg, 0.371 mmol) and PPh_3 (220 mg, 0.840 mmol) in toluene (70 mL) was added a solution of diethyl azodicarboxylate (130 mg, 0.747 mmol) in toluene (4 mL) dropwise. The solution was stirred at room temperature for 8 h, and then loaded onto a silica gel column and eluted with 0–10% EtOAc in hexanes to afford the macrocycle (176 mg, 87%). A single crystal suitable for X-ray crystallography analysis was obtained by slow cooling of a hot and concentrated 2-propanol solution of the macrocycle. The isolated yield and analytical data are reported for material judged >95% pure as determined by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.99-7.59 (m, 4H), 7.11 (s, 1H), 5.90 (s, 1H), 5.34 (m, 1H), 5.21 (m, 1H), 4.73 (dd, *J* = 7.0, 1.8 Hz, 1H), 3.24 (ddd, *J* = 16.7, 11.4, 5.6 Hz, 1H), 3.14-3.05 (m, 3H), 2.70 (m, 2H), 2.31 (d, *J* = 11.4, 6.2 Hz, 2H), 2.05 (m, 1H), 1.90 (m, 2H), 1.77 (m, 1H), 1.23 (m, 2H), 1.16 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), -0.03 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 156.7, 148.1, 137.1, 133.3, 133.2, 131.4, 130.8, 130.7, 129.6, 129.2, 124.0, 104.2, 66.0, 47.2, 41.7, 36.1, 27.6, 27.0, 26.5, 26.1, 25.7, 25.6, 18.1, -5.0, -5.1. $[\alpha]^{23}_{D}$ = 10.9 (*c* 1.69, $CHCl_3$). **IR** (DCM):

3058, 3004, 2954, 2857, 1592, 1548, 1471, 1373, 1265 cm^{-1}. **HRMS-ESI**: calculated for $[C_{27}H_{40}N_2O_6SSi+Na]^+$ 571.2269; found 571.2250.



19 6

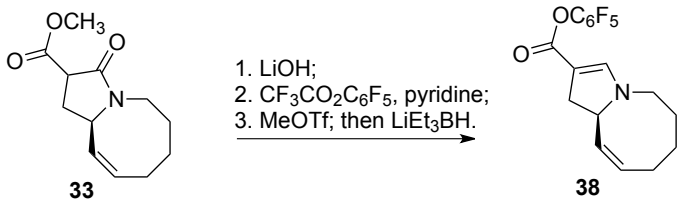
(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-triene (**6**). A mixture of macrocycle **19** (113 mg, 0.206 mmol), K_2CO_3 (60.8 mg, 0.44 mmol) and PhSH (41.5 mg, 0.38 mmol) in DMF (0.40 mL) was stirred at rt overnight. The reaction mixture was diluted with diethyl ether. The organic layer was washed with K_2CO_3 (aq), brine, dried over K_2CO_3 (s), and concentrated to give macrocyclic amine **6** (71.6 mg, 0.197 mmol, 96%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.16 (bs, 1H), 5.99 (s, 1H), 5.46 (m, 1H), 5.38 (m, 1H), 4.81 (dd, *J* = 6.7, 3.8 Hz, 1H), 2.70 (m, 3H), 2.50-2.56 (m, 3H), 2.36 (m, 2H), 1.87- 1.99 (m, 4H), 1.25-1.33 (m, 2H), 1.25 (bs, H), 0.97 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), -0.01 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 156.7, 137.1, 130.6, 129.4, 129.1, 105.1, 66.9, 47.9, 43.4, 36.8, 27.7, 26.9, 26.5, 26.4, 25.8, 18.1, -4.96. **$[\alpha]^{23}_D$** = +17.2 (*c* 0.37, $CHCl_3$). **IR** ($CDCl_3$ film): 3345, 3156, 3007, 2930, 2857, 1472, 1257, 1094 cm^{-1}. **HRMS-ESI**: calculated for $[C_{21}H_{37}NO_2Si+H]^+$ 364.2666; found 364.2669.



6 29

(*Z*)-2-chloro-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-trien-5-ium chloride (**29**). A HCl solution in HOAc (~ 1.5 M) was prepared by mixing AcCl (0.42 mL) and H_2O (0.10g) in HOAc (3.6 g). Macrocyclic amine **6** (15 mg, 0.041 mmol) was

dissolved in this HCl solution in HOAc (0.10 mL) and stirred for 3h at rt. The reaction mixture was concentrated by bubbling N_2 through, then concentrated under high vacuum to give the salt (13 mg, 0.04 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.76 (br s, 1H), 8.81 (br s, 1H), 7.56 (s, 1H), 6.13 (s, 1H), 5.41–5.30 (m, 3H), 3.00 (m, 1H), 2.87 (m, 2H), 2.81-2.75 (m, 3H), 2.67-2.74 (m, 1H), 2.42-2.50 (m, 2H), 2.29 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H), 1.37 (m, 1H), 1.23 (m, 1H), 1.09 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 158.0, 140.1, 130.0, 129.8, 124.4, 104.3, 50.6, 45.2, 41.2, 34.3, 27.6, 26.7, 26.2, 25.7, 22.8. **IR** ($CDCl_3$ film): 3392, 2954, 2784, 1589, 1549, 1456 cm^{-1}. **HRMS-ESI**: calculated for $[C_{15}H_{23}ClNO]^+$ 268.14627; found 268.14634.

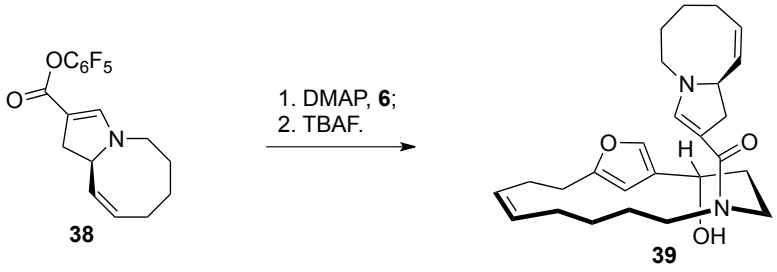


33 38

(*R*,*Z*)-perfluorophenyl 1,5,6,7,8,10a-hexahydropyrrolo[1,2-*a*]azocine-2-carboxylate (**38**). A mixture of malonate **33** (128 mg, 0.57 mmol) and LiOH (43 mg) was stirred in THF/H_2O (2.0/0.4 mL) at 0 °C for 1h. The reaction was quenched with 1 M $NaHSO_4$ (aq), extracted with DCM, dried over Na_2SO_4 and filtered through silica gel, further elution with EtOAc afforded the analytically pure carboxylic acid (120 mg, quant.).

To a solution of the carboxylic acid from above and pyridine (0.13 mL) in DMF (1.6 mL) at 0 °C was added pentafluorophenyl trifluoroacetate (0.16 mL, 0.91 mmol). After 2 h, the reaction mixture was diluted with EtOAc and washed successively with 1 M $NaHSO_4$, pH=7 phosphate buffer and brine, dried over Na_2SO_4 and concentrated under high vacuum to give the activated ester (214 mg, 99%).

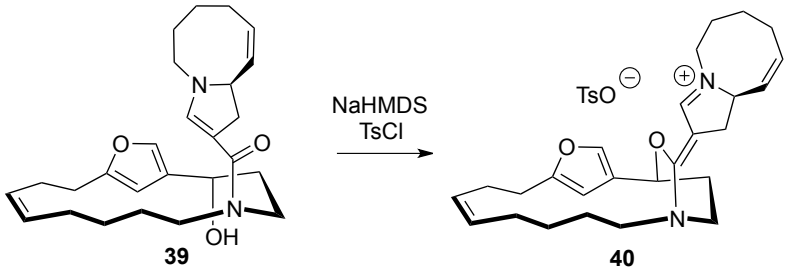
A CD_2Cl_2 (0.40 mL) solution of the ester (52 mg, 0.139 mmol) in a NMR tube was cooled to -78 °C, evacuated under vacuum, and refilled with N_2. MeOTf (0.0185 mL, 0.164 mmol) was added via syringe. The mixture was heated in a 40 °C oil bath for 2d, and cooled to -78 °C. $LiEt_3BH$ (0.165 mL, 1 M in THF, 0.165 mmol) was added and the mixture was kept at -78 °C for 2h, warmed to rt and quenched with 2 drops $NaHCO_3$(sat.). The mixture was dried over Na_2SO_4 and filtered through neutral alumina, eluted with 20% EtOAc in hexanes to give product (35 mg, 0.097 mmol, 70%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36 (s, 1H), 5.85 (app q, J =9.0 Hz, 1H), 5.56 (dd, J = 11.0, 7.0 Hz, 1H), 3.41 (m, 2H), 3.21 (dd, J = 13.9, 11.7 Hz, 1H), 2.74 (dd, J = 14.3, 9.2 Hz, 1H), 2.43 (m, 1H), 2.20 (m, 1H), 1.82 (m, 1H), 1.73 (m, 2H), 1.53 (m, 1H), 0.89 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 154.6, 132.3, 130.0, 93.1, 60.7, 49.0, 34.8, 27.0, 26.9, 25.7. **$[\alpha]^{23}_D$** = −154 (*c* 0.53, $CHCl_3$). **IR** (film): 3006, 2979, 2935, 2873, 1713, 1580, 1520, 1446, 1384, 1216 cm^{-1}. **HRMS-ESI**: calculated for ($C_{17}H_{14}F_5NO_2$+H) 360.1017, found 360.1034.



38 **39**

((*R*,*Z*)-1,5,6,7,8,10a-hexahydropyrrolo[1,2-*a*]azocin-2-yl)((*R*,*Z*)-2-hydroxy-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-trien-5-yl)methanone (**39**). A mixture of **38** (52 mg, 0.15 mmol), macrocyclic amine **6** (58 mg, 0.16 mmol), DMAP (6.0 mg, 0.049 mmol) and BHT (3.5 mg, 0.016 mmol) was stirred in DMF (0.050 mL) for 2 d. The reaction mixture was then concentrated under high vacuum. The residue was stirred with TBAF (0.40 mL, 1 M in THF, 0.40 mmol) for 1h at rt. The mixture was concentrated via

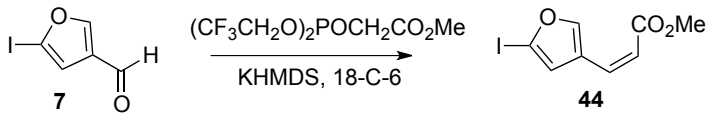
rotavapor and the residue was purified by flash column chromatography with 0-5% CH_3OH in EtOAc to give product **39** (25 mg, 0.059 mmol, 40%, 2 steps). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.11 (s, 1H), 6.68 (s, 1H), 5.88 (s, 1H), 5.71 (m, 1H), 5.56 (m, 1H), 5.36 (m, 1H), 5.22 (m, 1H), 4.76 (m, 1H), 4.27 (m, 1H), 3.94 (m, 1H), 3.25 (m, 2H), 3.18 (m, 1H), 3.06 (m, 1H), 2.87 (m, 2H), 2.69 (m, 3H), 2.56 (m, 1H), 2.33 (m, 3H), 2.15 (m, 2H), 1.95-2.06 (m, 5H), 1.72 (m, 2H), 1.64 (m, 1H), 1.53 (m, 1H), 1.21 (m, 2H), 0.97 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 168.1, 156.1, 149.6, 136.6, 131.2, 130.6, 130.2, 130.1, 129.9, 104.7, 102.1, 65.0, 61.4, 49.8, 49.1, 44.3, 38.8, 35.3, 28.3, 27.7, 27.4, 27.0, 26.2, 26.1, 25.8, 25.2. **$[\alpha]^{23}_D$** = 7.5 (*c* 0.62, $CHCl_3$). **IR** (film): 3327, 3016, 2932, 2858, 1589, 1549, 1444, 1370 cm^{-1}. **HRMS-ESI**: calculated for ($C_{26}H_{36}N_2O_3$+H) 425.2799, found 425.2809.



39 **40**

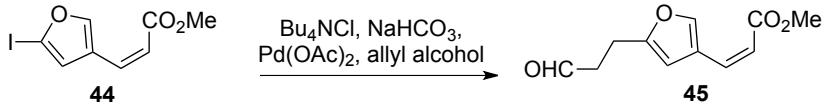
***O*-alkylation product 40**. To a solution of the alcohol (25 mg, 0.059 mmol) in THF (0.20 mL) in an ice bath was added NaHMDS (0.080 mL, 1 M in THF, 0.080 mmol) dropwise via syringe. After 5 min, TsCl (16.5 mg, 0.087 mmol) in THF (0.20 mL+0.10 mL rinse) was added via cannula. After 30 min, the reaction mixture was warmed to rt and stirred overnight. The volatiles were removed under vacuum and the residue was extracted with $CHCl_3$, filtered through Celite and the filtrate was concentrated. The residue was washes with diethyl ether and the remaining residue was extracted with EtOAc and $CHCl_3$, and filtered through Celite. The filtrate was concentrated to give the

product (27.3 mg, 0.047 mmol, 79%). A single crystal was obtained by slow diffusion of diethyl ether vapor to a $CHCl_3$ solution. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.24 (bs, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.99 (app q, *J* = 9.0 Hz, 1H), 5.93 (s, 1H), 5.49 (s, 1H), 5.32-5.45 (m, 3H), 4.75 (app q, *J* = 9.9 Hz, 1H), 3.82 (m, 2H), 3.59 (m, 1H), 3.47 (dd, *J* = 14.3, 8.8 hz, 1H), 3.35 (m, 2H), 3.25 (m, 1H), 2.68 (m, 4H), 2.49 (m, 1H), 2.40 (m, 1H), 2.31 (s, 3H), 2.19 (m, 2H), 1.94 (m, 2H), 1.75 (m, 4H), 1.62 (m, 2H), 1.44-1.30 (m, 6H), 0.61 (m, 1H), 0.43 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 162.4, 159.7, 157.6, 143.8, 138.8, 137.5, 135.5, 130.1, 129.3, 128.6, 128.3, 128.2, 126.2, 125.9, 122.6, 104.4, 91.6, 70.1, 60.4, 52.7, 48.9, 43.8, 35.6, 27.6, 27.5, 27.04, 27.01, 26.7, 26.6, 26.4, 26.1, 24.4, 21.2. **$[\alpha]^{23}_D$** = −271 (*c* 0.38, $CHCl_3$). **IR** (film): 3018, 2938, 2860, 1600, 1556, 1433, 1216, 1122, 1034, 1011 cm^{-1}. **HRMS-ESI**: calculated for ($C_{26}H_{34}N_2O_2$) 407.2693, found 407.2699.



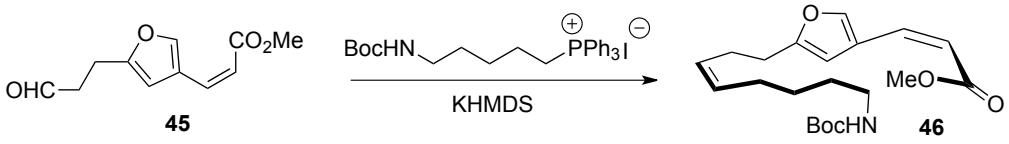
(*Z*)-methyl 3-(5-iodofuran-3-yl)acrylate (**44**). To a solution of $(CF_3CH_2O)_2POCH_2CO_2CH_3$ (2.23 g, 7.01 mmol) and 18-crown-6 (1.48 g, 5.61 mmol) in THF (30 mL) at -40 °C was added KHMDS (14.1 mL, 0.5 M in toluene, 7.05 mmol). After 30 min at this temperature, the solution was cooled to -78 °C and aldehyde **7** (1.54 g, 0.694 mmol) in THF (6 mL+4 mL rinse) was added via cannula. After 1h, TLC (hexanes/EtOAc 10:1) showed complete reaction. The reaction was quenched with $NaHCO_3$ (sat.) and extracted with diethyl ether. The organic layers were dried and concentrated. The residue was purified by flash column chromatography with 10% EtOAc in hexanes to give the product (1.85 g, 0.665 mmol, 96%). **^{1}H NMR** ($CDCl_3$, 500

MHz) δ 8.08 (s, 1H), 7.08 (s, 1H), 6.52 (d, *J* = 12.2 Hz, 1H), 5.72 (d, *J* = 12.2 Hz, 1H), 3.66 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 151.1, 132.1, 123.8, 122.1, 116.8, 89.1, 51.1. **IR** (film): 3020, 1720, 1638, 1439, 1216 cm^{-1}.



44 **45**

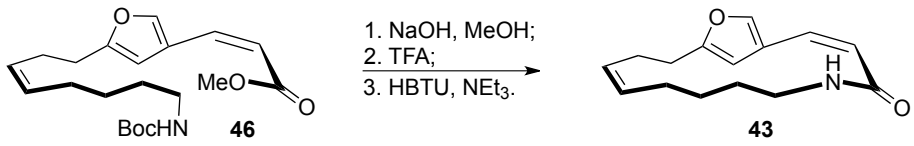
(*Z*)-methyl 3-(5-(3-oxopropyl)furan-3-yl)acrylate (**45**). A mixture of iodide **44** (1.85 g, 0.665 mmol), $NaHCO_3$ (1.44 g, 17.1 mmol), Bu_4NCl (1.94 g, 6.98 mmol), $Pd(OAc)_2$ (76 mg, 0.34 mmol) and allyl alcohol (0.80 mL, 12 mmol) in DMF (7.0 mL) was stirred at rt for 24h. The reaction mixture was diluted with diethyl ether (100 mL) and filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography with 10-15% EtOAc in hexanes to give aldehyde **45** as light yellow oil (0.84 g, 0.40 mmol, 61%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.77 (bs, 1H), 7.90 (s, 1H), 6.60 (d, *J* = 12.7 Hz, 1H), 5.72 (d, *J* = 12.2 Hz, 1H), 3.70 (s, 3H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.77 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 200.5, 166.5, 154.4, 146.0, 133.9, 122.0, 115.7, 51.1, 41.5, 20.4. **IR** (film): 3146, 2951, 2833, 2730, 1728, 1714, 1634, 1600, 1538, 1445, 1416 cm^{-1}. **HRMS-ESI**: calculated for ($C_{11}H_{12}O_4$+H) 209.0808, found 209.0838.



45 **46**

(*Z*)-methyl 3-(5-((*Z*)-8-((*tert*-butoxycarbonyl)amino)oct-3-en-1-yl)furan-3-yl)acrylate (**46**). To a cold (0 °C) suspension of $BocNH(CH_2)_5PPh_3I$ (4.02 g, 6.99 mmol) in THF (170 mL) was added dropwise KHMDS (13.5 mL, 0.5 M in toluene, 6.75 mmol). After 20 min, aldehyde **45** (1.30 g, 6.25 mmol) in THF (10 mL+5 mL rinse) was added via

syringe. After 10 min, no starting material was left as monitored by TLC (20% EtOAc in hexanes). The reaction was then quenched by addition of silica gel. The mixture was filtered through a glass frit and washed with diethyl ether. The filtrate was concentrated and the residue was purified by flash column chromatography with 5-8% EtOAc in hexans to give product **46** (1.88 g, 0.50 mmol, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.64 (d, *J* = 12.5 Hz, 1H), 6.60 (s, 1H), 5.72 (d, *J* = 12.5 Hz, 1H), 5.41 – 5.32 (m, 2H), 4.55 (bs, 1H), 3.72 (s, 3H), 3.07 (q, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.35 (q, *J* = 7.5 Hz, 2H), 2.00 (q, *J* = 6.7 Hz, 2H), 1.48 – 1.42 (m, 2H), 1.42 (s, 9H), 1.36 – 1.27 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 156.3, 155.9, 145.8, 134.3, 130.5, 128.3, 122.0, 115.3, 107.5, 78.9, 51.1, 40.4, 29.6, 28.4, 27.9, 26.75, 26.70, 25.6; **IR** (film) 3360, 2933, 2860, 1728, 1714, 1682, 1634, 1600, 1537, 1520, 1446, 1392, 1366, 1249, 1172, 1007, 921, 843, 780, 603 cm-1; **HRMS-ESI**: Exact mass calcd for $C_{21}H_{31}NO_5$ [M+Na]+: 378.2275; found: 378.2283.



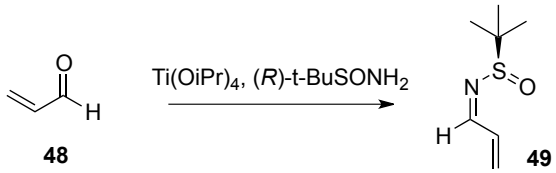
(2*Z*,10*Z*)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),2,10,14(17)-tetraen-4-one (**43**).[39] To a cooled (0 °C) solution of ester **46** (7.76 g, 20.6 mmol, 1.00 equiv.) in a mixture of MeOH/H_2O (340 mL/60 mL) was added NaOH (3 M) (68.5 mL, 206 mmol, 10.0 equiv.). After addition the ice-bath was removed and the reaction stirred at rt overnight. The reaction was cooled to 0 °C, quenched by addition of HCl (1 M) and the pH was adjusted to 1. The mixture was stirred at rt for 30 min, then the volatiles removed under reduced pressure and the aqueous phase extracted with EtOAc (3x). The combined

[39] This 3-step procedure was developed by Dr. Simone Bonazzi.

layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in mixture of hexanes/EtOAc (1:1) and purified by filtration through a SiO_2 plug. The cake was washed with a mixture of hexanes/EtOAc (1:1) and concentrated to afford the corresponding carboxylic acid (7.44 g, 20.4 mmol, 99%) as colorless oil. $\mathbf{R_f}$ = 0.63 (hexanes/EtOAc 6:4); **^{1}H NMR** (500 MHz, CD_3OD) δ 7.99 (s, 1H), 6.74 (d, *J* = 12.5 Hz, 1H), 6.65 (s, 1H), 5.76 (d, *J* = 12.6 Hz, 1H), 5.46 – 5.36 (m, 2H), 4.96 (s, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.40 (q, *J* = 7.1 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.52 – 1.45 (m, 2H), 1.45 (s, 9H), 1.39 – 1.29 (m, 2H); **^{13}C NMR** (125 MHz, CD_3OD) δ 170.4, 159.4, 158.3, 147.9, 135.9, 132.6, 130.3, 124.6, 117.9, 109.5, 80.6, 42.1, 31.4, 29.7, 29.7, 28.7, 28.7, 27.5; **IR** (film) 3323, 2932, 2855, 1694, 1651, 1633, 1531, 1514, 1454, 1392, 1367, 1247, 1169, 918, 835, 779 cm^{-1}; **HRMS-ESI**: Exact mass calcd for $C_{20}H_{29}NO_5$ $[M+Na]^+$: 364.2118; found: 364.2122.

To a cooled (0 °C) solution of the previously obtained carboxylic acid (1.89 g, 5.20 mmol, 1.00 equiv.) in DCM (15 mL) was added TFA (5.00 mL, 65.3 mmol, 12.6 equiv.). After addition the ice-bath was removed, the reaction stirred at rt for 45 min and then concentrated *in vacuo*. The residue was dissolved in MeOH, concentrated *in vacuo* and dried under high vacuum (3x cycle). The residue was dissolved in CH_3CN (2.60 L) and the solution heated to 50 °C. NEt_3 (3.30 mL, 23.4 mmol, 4.50 equiv.) and HBTU (5.90 g, 15.6 mmol, 3.00 equiv.) were sequentially added and the resulting mixture stirred at 50 °C for 24 h. The reaction was quenched by addition of saturated NH_4Cl, the volatiles removed under reduced pressure and the resulting mixture extracted with EtOAc (3x). The combined organic layers were washed with saturated NH_4Cl (1x), saturated Na_2CO_3 (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified on a Teledyne

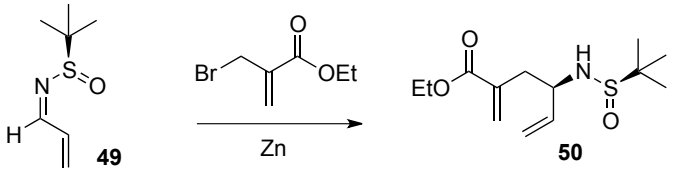
Isco CombiFlash® instrument (RediSepRf Gold High Performance column 80 g, hexane/EtOAc 6.5:3.5 to 2:8) to give macrolactam **43** (944 mg, 3.85 mmol, 74%) as a pale yellow solid. An analytical sample was recrystallized from MeOH and submitted to X-ray diffraction. **R*f*** = 0.48 (EtOAc 100%); **mp** = 125 – 126 ºC; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.42 (s, 1H), 6.49 (d, *J* = 12.0 Hz, 1H), 6.17 (d, *J* = 0.7 Hz, 1H), 5.95 (d, *J* = 12.1 Hz, 1H), 5.51 – 5.43 (m, 1H), 5.37 – 5.29 (m, 1H), 3.31 – 3.26 (m, 2H), 2.76 – 2.72 (m, 2H), 2.51 – 2.44 (m, 2H), 2.04 (q, *J* = 7.8 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.25 – 1.18 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.5, 157.5, 140.8, 131.0, 129.0, 125.8, 125.3, 122.0, 105.3, 38.8, 28.1, 27.9, 27.4, 26.6, 25.5; **IR** (neat) 3283, 2929, 2858, 1634, 1597, 1549, 1452, 1279, 1213, 1126, 960, 911, 800, 727 cm^{-1}; **HRMS-ESI**: Exact mass calcd for $C_{15}H_{19}NO_2$ $[M+H]^+$: 246.1489; found: 246.1494.



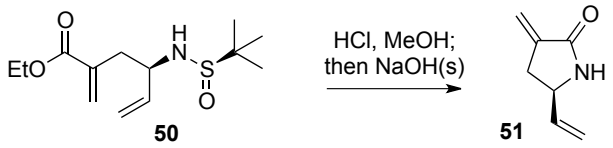
48 **49**

(*R*)-*N*-allylidene-2-methylpropane-2-sulfinamide (**49**). To a solution of acrolein (7.0 mL, 105 mmol) and (*R*)-tert-butyl sulfinamide (10.20 g, 84.3 mmol) in DCM (60 mL) was added $Ti(i\text{-}PrO)_4$ (74 mL, 237 mmol). The mixture was stirred at room temperature overnight and poured into ice/water. After standing for 30 min with occasionally shaking, the white suspension was filtered through Celite and rinsed with DCM. The filtrate was collected and the two layers were separated, the aqueous layer was extracted with DCM. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography with DCM gave the product as light yellow oil (13.0 g, 81.8 mmol, 97%). **R*f*** = 0.16 (DCM). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.19 (d, J = 9.3 Hz, 1H), 6.66 (dt, J = 17.6, 9.5 Hz, 1H), 5.98 (d, J = 11 Hz, 1H), 5.97 (d, J = 17

Hz, 1H), 1.18 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 163.93, 134.38, 131.24, 57.07, 22.19. **$[\alpha]^{23}_D$** = −583 (*c* 1.89, $CHCl_3$). **IR** (film): 2961, 2868, 1624, 1577, 1474, 1457 cm^{-1}. **HRMS-ESI**: calculated for $C_7H_{13}NOS$+H 160.0791, found 160.0790.

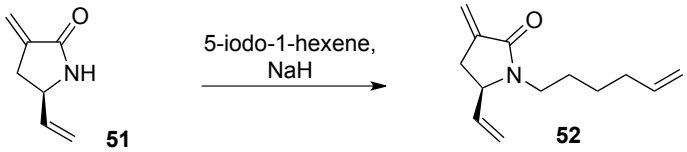


(*R*)-ethyl 4-((*R*)-1,1-dimethylethylsulfinamido)-2-methylenehex-5-enoate (**50**). To a suspension of zinc (2.57 g, 39.5 mmol) and LiCl (2.57 g, 60.6 mmol) in DMF (50 mL) was added a solution of bromide (8.13 g, 43.0 mmol), imine (3.18 g, 20.0 mmol) and H_2O (0.37 g, 20.6 mmol) in DMF (25 mL) via cannula, followed by a DMF rinse (25 mL). The reaction is exothermic and a water cooling bath was used. After stirring for 6h at room temperature, ^{1}H NMR analysis of an aliquot showed consumption of the imine. The reaction was quenched with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated. DMF was removed under high vacuum. The residue was purified by flash column chromatography with 30%-50% EtOAc in hexanes as eluent. The product was obtained as light yellow oil (4.50 g, 1.65 mmol, 82%). **R*f*** = 0.54 (EtOAc). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.21 (s, 1H), 5.84 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.57 (s, 1H), 5.23 (d, J= 17.1 Hz, 1H), 5.12 (d, J = 10.7 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.91 (pent, J = 7.1 Hz), 3.27 (d, J = 7.3 Hz), 2.60 (dd, J = 13.7, 7.8 Hz, 1H), 2.51 (dd, J = 13.7, 6.3 Hz, 1H), 1.26 (t, J = 7.3 Hz, 3H), 1.13 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.81, 139.15, 136.98, 127.82, 116.51, 60.74, 58.56, 55.95, 38.20, 22.44, 14.08. **$[\alpha]^{23}_D$** = −42.5 (*c* 2.33, $CHCl_3$). **IR** (film): 3214, 3080, 2981, 2870, 1712, 1631 cm^{-1}. **HRMS-ESI**: calculated for ($C_{13}H_{23}NO_3S$+Na) 296.1291, found 296.1282.



50 51

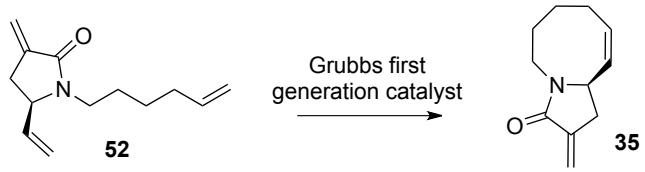
(*R*)-3-methylene-5-vinylpyrrolidin-2-one (**51**). A solution of HCl in CH_3OH (60 mL, 1.25 M, 75.0 mmol) was added to the sulfinamide (5.81 g, 21.3 mmol) and the resulting mixture was stirred at room temperature for 2h. When the reaction was complete, NaOH (5.0 g, 125 mmol) was added to the reaction mixture and stirring was continued for 1h. The reaction was quenched with H_2O and extracted with EtOAc, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography with 50% EtOAc in hexanes afforded the product (2.26 g, 1.84 mmol, 86%). **R*f*** = 0.38 (Et_2O); **mp** = 44 – 46 °C. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.86 (bs, 1H), 5.92 (s, 1H), 5.75 (m, 1H), 5.29 (s, 1H), 5.20 (d, J = 17 Hz, 1H), 5.07 (d, J = 10 Hz, 1H), 4.13 (app q, J = 6.5 Hz, 1H), 3.01 (dd, J= 17, 8 Hz, 1Hz), 2.48 (app d, J = 17 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.93, 138.93, 138.59, 115.87, 115.73, 53.51, 33.52. **$[\alpha]^{23}_D$** = −55.1 (*c* 2.96, $CHCl_3$). **IR** (film): 3434, 3215, 3089, 2988, 1698, 1662 cm^{-1}. **HRMS-ESI**: calculated for (C_7H_9NO+Na) 146.0576, found 146.0550.



51 52

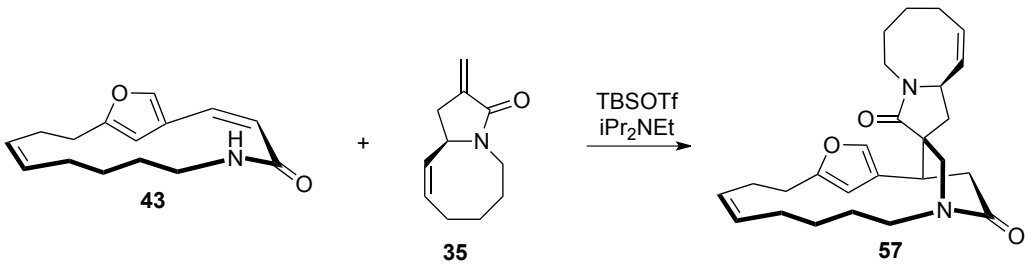
(*R*)-1-(hex-5-en-1-yl)-3-methylene-5-vinylpyrrolidin-2-one (**52**). A solution of the lactam (2.26 g, 18.4 mmol) and 1-iodo-5-hexene (4.80 g, 22.8 mmol) in DMF (36 mL) was cooled in an ice bath. NaH (1.60g, 60% suspension in oil, 40 mmol) was added slowly in one portion. ^{1}HNMR analysis of an aliquot showed the reaction was completed in 30 min. The reaction was quenched with H_2O and extracted with Et_2O, dried over

Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatrography with 30% EtOAc in hexanes afforded the diene as liquid (3.22 g, 15.7 mmol, 85%). **R*f*** = 0.42 (hexanes/EtOAc 7:3). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.98 (s, 1H), 5.77 (m, 1H), 5.61 (m, 1H), 5.30 (s, 1H), 5.26 (d, J = 17 Hz, 1H), 5.22 (d, J= 10 Hz, 1H), 4.99 (dt, J= 17, 1.7 Hz, 1H), 4.94 (d, J = 10Hz, 1H), 4.03 (td, J = 8.2, 4.1 Hz, 1H), 3.64 (app quint, J = 7 Hz, 1H), 2.98 (m, 2H), 2.46 (m, 1H), 2.06 (m, 2H), 1.55 (m, 1H), 1.49 (m, 1H), 1.38 (quint, J = 7.6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.50, 138.71, 138.13, 137.66, 118.06, 114.87, 114.51, 58.17, 40.52, 33.07, 31.77, 26.29, 25.87. **$[\alpha]^{23}_D$** = −87.4 (*c* 1.30, $CHCl_3$). **IR** (film): 3079, 2978, 2931, 1738, 1682, 1661, 1441, 1422 cm^{-1}. **HRMS-ESI**: calculated for ($C_{13}H_{29}NO$+Na) 228.1359, found 228.1361.



(*R*,*Z*)-2-methylene-1,5,6,7,8,10a-hexahydropyrrolo[1,2-*a*]azocin-3(2*H*)-one (**35**). A solution of the diene (1.60 g, 7.80 mmol) in DCM (4.0 L, ACS grade, new bottle) was deoxygenated by refluxing under N_2 for 30 min. Grubbs first generation catalyst (3×30 mg, 0.11 mmol, 1.5 mol%) in DCM was added via syringe in three equal portions every 3 hours. The reaction mixture was then refluxed overnight and concentrated under vacuum. The crude product was combined with the products from the other two batches (1.60 g and 1.25 g) and the desired product (3.19 g, 18 mmol, 83%) was obtained by flash column chromatography with 20-30% EtOAc in hexanes. **R*f*** = 0.65 (EtOAc 100%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.92 (bs, 1H), 5.79 (app q, J = 9 Hz, 1H), 5.37 (dd, J = 10, 6.5 Hz, 1H), 5.26 (bs, 1H), 4.29 (app q, J = 6.5 Hz, 1H), 3.57 (dd, J = 14, 7.8 Hz, 1H), 3.42 (dd, J = 14, 9.6 Hz, 1H), 2.97 (m, 1H), 2.45 (m, 1H), 2.23 (m, 1H), 2.11 (m, 1H),

1.86 (m, 1H), 1.62 (m, 2H), 1.50 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.37, 139.73, 132.38, 130.06, 114.90, 53.30, 41.53, 32.64, 27.27, 25.79, 25.36. **$[\alpha]^{23}_D$** = −139 (*c* 2.30, $CHCl_3$). **IR** (film): 3013, 2928, 2857, 1682, 1660, 1417 cm^{-1}. **HRMS-ESI**: calculated for ($C_{11}H_{15}NO$+Na) 228.1359, found 228.1361.



Bisamide 57.[40] To a cooled (0 °C) suspension of macrolactam (**43**) (1.12 g, 4.60 mmol, 1.05 equiv.) in DCE (14 mL) were sequentially added *i*-Pr2NEt (1.36 mL, 7.80 mmol, 1.80 equiv.) and TBSOTf (2.00 mL, 8.70 mmol, 2.00 equiv.). The suspension turned in to a clear yellow solution. The ice-bath was removed and a solution of bicyclic lactam (**35**) (0.76 g, 4.30 mmol, 1.00 equiv.) in DCE (1.5 mL, final reaction concentration 0.28 M vs **35**) was added via syringe pump at the rate of 500 μL/h. After addition the reaction was stirred at rt for 14 h, then quenched by addition of diluted HCl (0.5 M) and the mixture extracted with DCM (3x). The combined layers were washed with saturated $NaHCO_3$ (1x), dried (Na_2SO_4) and concentrated *in vacuo*. Two diastereoisomers were observed and a diastereomeric ratio of 9:1 was determined by ^{1}H-NMR (C12 proton signal) prior to purification. The product was purified on a Teledyne Isco CombiFlash® instrument (RediSepRf Gold High Performance column 40 g, hexane/EtOAc 5:5 to 0:10) to give bislactam **57** (1.43 g, 3.38 mmol, 79%) and the minor diastereoisomer **58** (130 mg, 0.31 mmol, 7%) as white solids. An analytical sample of bis-lactam **57** and diastereoisomer **58**

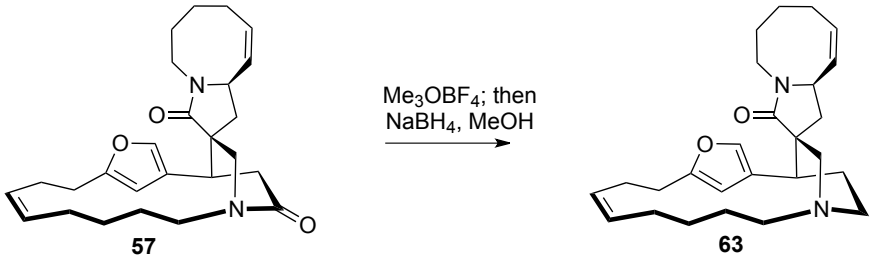
[40] This procedure was developed by Dr. Simone Bonazzi.

were recrystallized from Et_2O and submitted to X-ray diffraction.

Bislactam 57: R_f = 0.32 (EtOAc/MeOH 9:1); **mp** = 99 – 102 ºC; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.10 (s, 1H), 6.07 – 6.03 (m, 1H), 6.06 (d, *J* = 1.4 Hz, 1H), 5.63 – 5.56 (m, 1H), 5.46 (dd, *J* = 10.8, 7.0 Hz, 1H), 5.36 (dt, *J* = 11.0, 7.1 Hz, 1H), 4.66 – 4.61 (m, 1H), 4.44 (ddd, *J* = 13.1, 9.6, 3.1 Hz, 1H), 4.13 (d, *J* = 12.9 Hz, 1H), 3.71 (dd, *J* = 14.1, 8.8 Hz, 1H), 3.24 (d, *J* = 7.2 Hz, 1H), 3.12 (dd, *J* = 14.2, 8.4 Hz, 1H), 3.07 – 3.03 (m, 1H), 3.04 (d, *J* = 13.0 Hz, 1H), 2.79 – 2.76 (m, 2H), 2.72 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.67 (ddd, *J* = 13.5, 6.1, 3.0 Hz, 1H), 2.53 – 2.47 (m, 2H), 2.41 (dd, *J* = 18.4, 1.2 Hz, 1H), 2.37 – 2.26 (m, 2H), 2.26 – 2.17 (m, 1H), 2.16 – 2.07 (m, 1H), 2.04 – 1.96 (m, 1H), 1.91 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.86 – 1.70 (m, 3H), 1.65 – 1.43 (m, 4H); **^{13}C NMR** (125 MHz, CD_3OD) δ 175.4, 171.7, 159.0, 140.5, 137.2, 132.7, 131.0, 130.8, 126.6, 106.6, 55.2, 54.0, 50.7, 50.0, 42.6, 41.4, 38.0, 34.6, 29.6, 29.4, 29.3, 28.9, 28.5, 28.3, 27.9, 25.8; **IR** (neat) 2994, 2931, 2860, 1682, 1634, 1494, 1454, 1422, 1360, 1237, 1180, 1106, 964, 936, 903, 751, 665 cm^{-1}; **HRMS-ESI**: Exact mass calcd for $C_{26}H_{34}N_2O_3$ $[M+H]^+$: 423.2642; found: 426.2650; $[\alpha]_D^{21.9}$ = –138.6 (c = 1.18, MeOH).

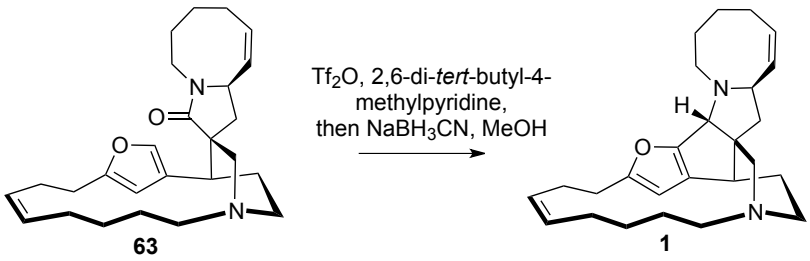
Diastereoisomer 58: R_f = 0.25 (EtOAc/MeOH 9:1); **mp** = 95 – 97 ºC; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.14 (s, 1H), 6.10 (d, *J* = 0.9 Hz, 1H), 5.90 – 5.84 (m, 1H), 5.71 (dd, *J* = 11.3, 4.9 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.37 (dt, *J* = 11.0, 7.1 Hz, 1H), 4.46 (ddd, *J* = 13.2, 9.6, 3.3 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.64 (ddd, *J* = 13.5, 10.5, 2.6 Hz, 1H), 3.33 – 3.28 (m, 2H), 3.02 (dd, *J* = 12.7, 1.5 Hz, 1H), 3.01 – 2.97 (m, 1H), 2.82 – 2.78 (m, 2H), 2.69 (ddd, *J* = 13.5, 6.1, 3.1 Hz, 1H), 2.54 – 2.49 (m, 3H), 2.46 (dd, *J* = 13.1, 8.7 Hz, 1H), 2.39 (dd, *J* = 18.4, 1.2 Hz, 1H), 2.27 – 2.18 (m, 3H), 2.14 – 2.07 (m, 1H), 1.91 – 1.73 (m, 4H), 1.73– 1.67 (m, 2H), 1.62 – 1.53 (m, 1H), 1.50 – 1.41

(m, 1H); **^{13}C NMR** (125 MHz, CD_3OD) δ 175.9, 171.7, 158.9, 140.8, 133.8, 132.6, 131.9, 131.0, 126.7, 106.8, 56.7, 54.7, 50.1, 49.5, 44.3, 40.3, 38.1, 36.7, 29.6, 28.9, 28.9, 28.5, 27.9, 26.5, 26.3, 25.9; **IR** (film) 3007, 2932, 2860, 1682, 1644, 1548, 1494, 1434, 1349, 1285, 1235, 965, 935, 904, 752, 665 cm^{-1}; **HRMS-ESI**: Exact mass calcd for $C_{26}H_{34}N_2O_3$ $[M+H]^+$: 423.2642; found: 423.2644; **$[\alpha]_D^{21.5}$** = +23.2 (c = 1.00, MeOH).



Lactam 63. To a suspension of Me_3OBF_4 (315 mg, 2.13 mmol, 3.00 equiv.) in DCM (7.1 mL) were sequentially added 4Å sieves (3.00 g) and bis-lactam **57** (300 mg, 0.71 mmol, 1.00 equiv.). The mixture was stirred at rt for 2 h, then filtered under N2 and the sieves washed with dry DCM (10 mL). The solution was cooled to 0 °C and dry MeOH (20 mL) was added. $NaBH_4$ (537 mg, 14.2 mmol, 20.0 equiv.) was added in two portions and the resulting mixture was stirred for 10 min at 0 °C and then for 1 h at rt. The reaction was quenched by addition of saturated NH_4Cl, stirred at rt for 15 min and then the volatiles removed under reduced pressure. The mixture was poured into a saturated Na_2CO_3 solution, extracted with EtOAc (4x) and the combined layers dried (Na_2SO_4) and concentrated *in vacuo*. The product was recrystallized from EtOH, the solid collected by filtration and washed with a small amount of cold (0 °C) EtOH to give compound **2** (200 mg, 0.48 mmol) as a white crystalline solid. The filtrate was concentrated and purified by column chromatography on SiO_2 (hexane/EtOAc 4:6 to 0:10, then EtOAc/MeOH 10:0 to 96:4) to give an additional portion of product **63** (21.8 mg, 0.05 mmol, 76% overall

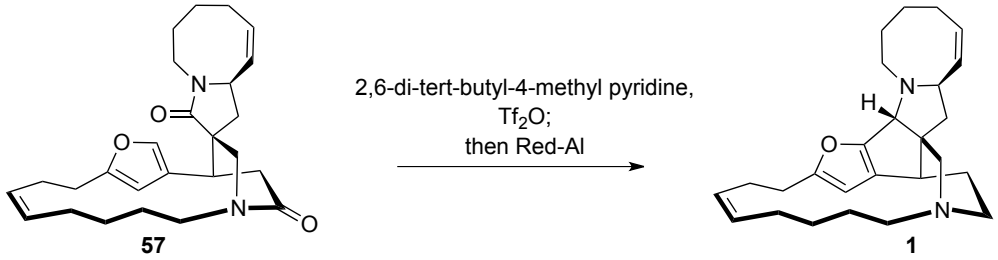
yield). An analytical sample was recrystallized from MeOH and submitted to X-ray diffraction. **R*f*** = 0.39 (EtOAc/MeOH 7.5:2.5); **mp** = 159 – 161 ºC; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.05 (s, 1H), 6.69 (d, *J* = 1.3 Hz, 1H), 6.04 (dt, *J* = 10.7, 8.4 Hz, 1H), 5.55 – 5.49 (m, 1H), 5.40 (dd, *J* = 10.8, 7.3 Hz, 1H), 5.38 – 5.33 (m, 1H), 4.57 – 4.52 (m, 1H), 3.69 (dd, *J* = 11.7, 1.1 Hz, 1H), 3.68 – 3.65 (m, 1H), 3.23 – 3.17 (m, 1H), 2.98 (dd, *J* = 6.0, 2.3 Hz, 1H), 2.97 – 2.94 (m, 1H), 2.78 – 2.58 (m, 6H), 2.47 – 2.41 (m, 1H), 2.36 – 2.26 (m, 3H), 2.26 – 2.19 (m, 1H), 2.17 (d, *J* = 11.7 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.01 – 1.94 (m, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.70 (m, 4H), 1.74 (dd, *J* = 12.7, 9.2 Hz, 2H), 1.69 – 1.62 (m, 1H), 1.53 – 1.42 (m, 2H); **^{13}C NMR** (125 MHz, CD_3OD) δ 178.1, 157.3, 139.5, 137.5, 132.0, 131.8, 130.7, 129.5, 110.9, 57.3, 56.7, 53.8, 51.6, 46.9, 43.7, 42.3, 33.8, 30.6, 30.0, 29.9, 29.4, 28.9, 28.6, 28.5, 26.9, 25.9; **IR** (film) 3004, 2923, 2857, 2791, 1558, 1444, 1386, 1357, 1330, 1277, 1238, 1132, 1081, 953, 936, 850, 794, 756, 726 cm-1; **HRMS-ESI**: Exact mass calcd for $C_{26}H_{36}N_2O_2$ [M+H]+: 409.2850; found: 409.2859; **$[\alpha]_D^{22.2}$** = –86.9 (c = 0.88, MeOH).



(–)-Nakadomarin A (**1**).[41] To a solution of lactam **63** (210 mg, 0.51 mmol, 1.00 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (423 mg, 2.06 mmol, 4.00 equiv.) in DCM (10 mL) was added Tf_2O (259 μL, 1.54 mmol, 3.00 equiv.) via syringe pump over a 30 min period. After addition the reaction was stirred at rt for an additional 30 min, then dry

[41] This 2-steps procedure was developed by Dr. Simone Bonazzi.

MeOH (10 mL) and $NaCNBH_3$ (641 mg, 10.2 mmol, 20.0 equiv.) were added. The resulting solution was stirred at rt overnight, then quenched by addition of saturated Na_2CO_3. The volatiles were removed under reduced pressure and the mixture extracted with EtOAc (3x). The combined layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude was dissolved in Et_2O, the precipitate removed by filtration and the filtrate concentrated. The product was purified on a Teledyne Isco CombiFlash® instrument (RediSepRf Gold C18 column (15.5 g, 20 – 40 μm), H_2O/MeOH 2:8 to 1:9) to give (–)-nakadomarin A (**1**) (105 mg, 0.27 mmol, 52%) as a colorless solid.



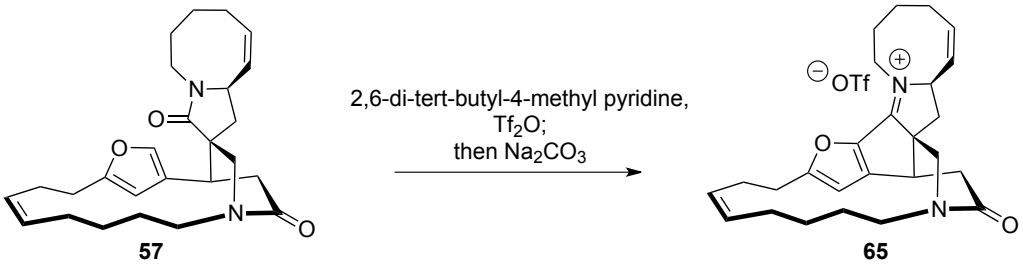
To a solution of amide **57** (84 mg, 0.20 mmol) and 2,6-di-tert-butyl-4-methyl pyridine (167 mg, 0.82 mmol) in DCM (4.0 mL) was added Tf_2O (0.125 mL, 0.74 mmol) dropwise. The reaction mixture was stirred at room temperature for 2h. Vitride® (2.0 mL, 65% in toluene) was then added dropwise at −78 °C. The reaction mixture was warmed to rt and stirred for 1h and then 60 °C for 2h, and cooled to −78 °C. The reaction was quenched by adding acetic acid (0.80 mL) dropwise, and then stirred for 10 min at rt. DCM was added, followed by saturated Rochelle's salt and Na_2CO_3 (aq). The mixture was stirred for 30 min until clear solution was obtained. The aqueous layer was extracted with DCM and organic layer was dried over Na_2SO_4, concentrated under vacuum. Purification by flash column chromatography with DCM to EtOAc to 30% MeOH in EtOAc afforded the natural product (58 mg, 0.15 mmol, 74%). On a larger scale (500 mg,

1.18 mmol bisamide **57**), (–)-nakadomarin A was obtained in 69% yield (317 mg, 0.81 mmol). **R*f*** = 0.15 (EtOAc/MeOH 7.5:2.5); **^{1}H NMR** (600 MHz, CD_3OD) δ 5.89 (s, 1H), 5.85 – 5.80 (m, 1H), 5.56 – 5.50 (m, 1H), 5.50 – 5.45 (m, 1H), 5.33 – 5.26 (m, 1H), 3.95 (s, 1H), 3.77 – 3.71 (m, 1H), 3.08 – 3.01 (m, 1H), 3.07 (d, *J* = 12.1 Hz, 1H), 2.86 (br s, 1H), 2.84 – 2.78 (m, 1H), 2.75 (ddd, *J* = 14.2, 7.1, 2.3 Hz, 1H), 2.69 – 2.62 (m, 2H), 2.56 – 2.49 (m, 1H), 2.44 (dt, *J* = 11.8, 3.7 Hz, 1H), 2.39 – 2.33 (m, 2H), 2.34 (d, *J* = 12.3 Hz, 1H), 2.23 – 2.14 (m, 2H), 2.14 – 2.08 (m, 1H), 2.08 – 2.00 (m, 1H), 1.98 – 1.91 (m, 1H), 1.93 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.85 (ddd, *J* = 14.2, 7.2, 2.8 Hz, 1H), 1.78 – 1.59 (m, 4H), 1.51 (dd, *J* = 12.2, 10.1 Hz, 1H), 1.47 – 1.39 (m, 1H), 1.39 – 1.33 (m, 1H), 1.15 – 1.05 (m, 2H), 0.97 – 0.86 (m, 1H); **^{13}C NMR** (125 MHz, CD_3OD) δ 163.1, 157.6, 135.8, 135.2, 133.1, 132.6, 130.1, 105.6, 75.5, 64.5, 61.5, 60.1, 59.0, 51.8, 46.9, 44.4, 44.0, 30.4, 30.1, 30.1, 29.7, 28.1, 28.0, 26.8, 26.8, 23.9; **IR** (film) 3005, 2923, 2857, 2792, 1694, 1556, 1444, 1386, 1354, 1330, 1280, 1239, 1133, 1081, 1063, 953, 936, 850, 793, 756, 726 cm^{-1}; **HRMS-ESI**: Exact mass calcd for $C_{26}H_{36}N_2O$ [M+H]+: 393.2900; found: 393.2906; **$[\alpha]_D^{21.5}$** = –64.3 (c = 0.31, MeOH). Lit.[42] **$[\alpha]_D^{25}$** = –65.6 (c = 0.66, MeOH); HPLC-MS: Column: Phenomenex Kinetex 2.6 μm, C-18, 100 Å, 100 x 2.1 mm. Solvent system: A: 95% water, 5% CH_3CN, 0.1% HCO_2H, 2 mM NH_4OAc. B: 95% CH_3CN, 5% water, 0.1% HCO_2H, 2 mM NH_4OAc. Flow rate: 0.400 mL/min. Gradient: 1% B (*t* = 0 min), 30% B (*t* = 0.5 min), 100% B (*t* = 4.0 min), 100% B (*t* = 5.0 min), 1% B (*t* = 6.1 min), 1% B (*t* = 8.1 min). (–)-nakadomarin A (1): t_r 2.38 min (254 nm). ESI-MS for [M+H]+: 393 m/z.

[42] Jakubec, P.; Cockfield, D.; Dixon, D. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

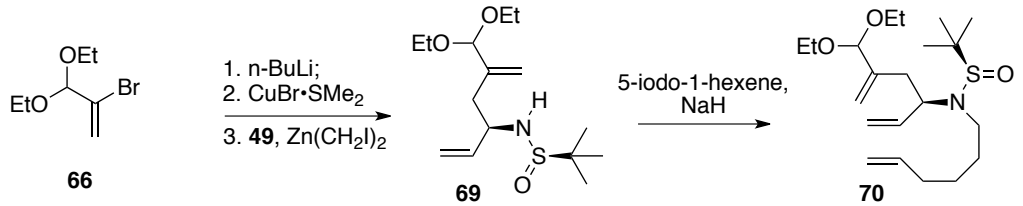
Comparison of observed ^{13}C NMR signals for synthetic (–)-nakadomarin A.

Nishida (*Angew. Chem. Int. Ed.* **2004**, *42*, 2020)	Funk (*Org. Lett.* **2010**, *12*, 4912)	Dixon (*J. Am. Chem. Soc.* **2009**, *131*, 16632)	Evans (49.0 ppm for C**H**D_2OD)
23.0	23.0	23.0	22.9
25.8	25.8	25.9	25.6
25.9	25.9	26.0	25.9
27.1	27.1	27.1	27.1
27.2	27.2	27.2	27.2
28.8	28.8	28.8	28.8
29.1	29.1	29.2	29.0
29.2	29.2	29.2	29.2
29.5	29.5	29.5	29.5
43.1	43.1	43.1	42.9
43.4	43.4	43.4	43.2
46.1	46.1	46.1	46.1
50.9	50.9	50.9	51.0
58.4	58.3	58.3	58.7
59.3	59.3	59.3	59.2
60.6	60.6	60.6	60.5
63.6	63.6	63.6	63.6
74.8	74.7	74.7	74.8
104.8	104.7	104.8	104.8
129.3	129.3	129.3	129.2
131.3	131.4	131.5	131.0
132.2	132.2	132.3	132.2
134.8	134.7	134.7	135.1
135.4	135.3	135.3	135.8
156.3	156.4	156.4	155.7
162.6	162.5	162.5	162.7



57 **65**

To a solution of bisamide **57** (20 mg) and 2,6-di-tert-butyl-4-methyl pyridine (32 mg, mmol) in DCM (1.6 mL) was added Tf_2O (0.022 mL) dropwise. The mixture was stirred at rt for 2h, and then quenched with Na_2CO_3 (aq) and extracted with DCM, dried over Na_2SO_4, concentrated and filtered through silica gel, eluted with DCM, then DCM/MeOH (20:1) to obtain the product (25 mg, 95%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.39 (s, 1H), 5.88 (app q, *J* = 9.0 Hz, 1H), 5.76(dd, *J*= 11.5, 4.6 Hz, 1H), 5.33 (m, 3H), 4.21 (m, 1H), 4.07 (dd, *J* = 13.3, 11.9 Hz, 1H), 3.97 (ddd, *J* = 16.9, 11.0, 3.2 Hz, 1H), 3.83 (d, *J* = 14.7 Hz, 1H), 3.70 (bs, 1H), 3.58 (d, *J* = 14.7 Hz, 1H), 3.35 (dd, *J* = 12.8, 9.2 Hz, 1H), 3.06 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.61-2.79 (m, 4H), 2.44 (dt, *J* = 13.7, 3.7 Hz, 1H), 2.36 (m, 2H), 2.25 (m, 1H), 2.18 (m, 1H), 2.08 (d, *J* = 12.8 Hz, 1H), 1.84 (m, 3H), 1.62-1.76 (m, 2H), 1.28 (m, 1H), 1.05 (m, 1H), 0.75 (m, 1H), 013 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 177.6, 170.6, 169.8, 168.2, 142.7, 132.4, 130.4, 129.2, 125.7, 110.0, 73.1, 66.2, 55.2, 51.9, 46.8, 41.2, 39.0, 33.6, 29.82, 29.77, 28.5, 27.6, 26.4, 25.0, 23.7, 23.3. **$[\alpha]^{23}_D$** = −137 (*c* 1.54, $CHCl_3$). **IR** (film): 3013, 2947, 2862, 1694, 1667, 1553, 1499, 1451, 1428, 1328, 1270, 1223, 1158, 1030 cm^{-1}. **HRMS-ESI**: calculated for ($C_{26}H_{33}N_2O_2$) 405.2537, found 405.2542.



66 **69** **70**

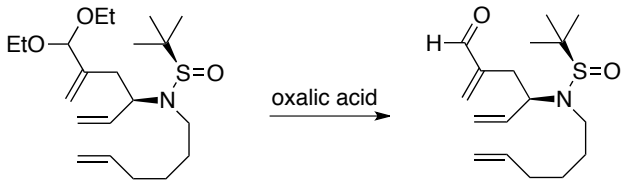
To a solution of 2-bromopropenal diethylacetal **66** (121 mg, 0.579 mmol) in THF (0.50 mL) at -78 °C was added *n*-BuLi (025 mL, 2.5 M in hexanes, 0.625 mmol) dropwise. After 30 min, $CuBr•SMe_2$ (130 mg, 0.632 mmol) was added and the mixture was warmed to -50 °C and stirred for 30 min at this temperature, the resultant clear cuprate solution was then cooled to -78 °C.

In a separate flask, Et_2Zn (0.70 mL, 1 M in hexanes, 0.70 mmol) was added dropwise to a solution of CH_2I_2 (0.39 g, 1.5 mmol) in THF (0.50 mL) at -78 °C. The mixture was stirred for 30 min at -78 °C, then 30 min at 0 °C to give the $Zn(CH_2I)_2$ solution.

Imine **49** (72 mg, 0.453 mmol) was added to the cuprate solution at -78 °C, followed by immediate addition of the $Zn(CH_2I)_2$ solution prepared above. The reaction mixture was stirred for 1h and the cooling bath temperature raised from -50 to -20 °C. The solution was then warmed to rt and quenched with basic NH_4Cl/NH_3 solution and diluted with EtOAc. The organic layer was washed with basic NH_4Cl/NH_3 solution until the aqueous layer colorless. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was further dried under high vacuum and used without further purification. An analytical pure sample could be obtained by flash column chromatography with 20-40% EtOAc in hexanes with trace amount of Et_3N. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.88 (ddd, *J* = 17.1, 10.3, 6.3 Hz, 1H), 5.27 (app. d, *J* = 17 Hz, 1H), 5.24 (s, 1H), 5.14 (app d, *J* = 10.3 Hz, 1H), 5.05 (s, 1H), 4.69 (s, 1H), 4.01 (quint, *J* = 6.8 Hz, 1H), 3.57 (m, 2H), 3.51 (d, *J* = 6.8 Hz, 1H), 3.43 (m, 2H), 2.37 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 6H), 1.17 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 141.7, 139.5, 116.5, 116.1, 103.5, 61.81, 61.88, 57.3, 55.7, 37.6, 22.4, 14.9. **$[\alpha]^{23}_D$** = −60.0 (*c* 1.35, $CHCl_3$). **IR** (film): 3227, 3079, 2977, 2873,

1644, 1475, 1444, 1417, 1390, 1364, 1329, 1117, 1062 cm^{-1}. **HRMS-ESI**: calculated for ($C_{15}H_{29}NO_3S$+Na) 326.1760, found 326.1776.

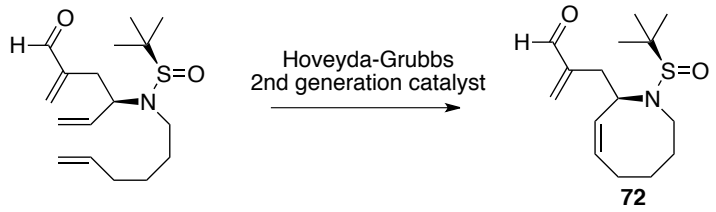
The crude allylation product was mixed with 1-iodo-5-hexene (146 mg, 0.695 mmol) in DMF (2.0 mL) and cooled to 0 °C. NaH (130 mg, 60% dispersion in oil, 3.25 mmol) was added in one portion. After 2.5 h at rt, the reaction was quenched with H_2O and extracted with diethyl ether, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography with 20% EtOAc in hexanes afforded the product (91 mg, 0.236 mmol, 52% over 2 steps). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.75 (m, 2H), 5.19 (s, 1H), 5.11 (app d, J = 17.6 Hz, 1H), 5.10 (app d, J = 11.1 Hz, 1H), 5.00 (s, 1H), 4.96 (app d, J = 17.0 Hz, 1H), 4.91 (app d, J = 11.1 Hz, 1H), 4.67 (s, 1H), 4.00 (bs, 1H), 3.53 (m, 2H), 3.40 (m, 2H), 3.11 (m, 1H), 2.71 (m, 1H), 2.61 (d, J =14.1 Hz, 1H), 2.43 (m, 1H), 2.01 (m, 2H), 1.61 (m, 1H), 1.47 (m, 1H), 1.32 (m, 2H), 1.12-1.17 (m, 15H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 142.5, 138.3, 137.8, 116.8, 115.6, 114.6, 103.6, 61.7, 60.7, 57.6, 42.8, 34.5, 33.3, 29.5, 26.4, 23.6, 15.0. $[\alpha]^{23}_D$ = +31.7 (*c* 2.17, $CHCl_3$). **IR** (film): 3078, 2976, 2930, 2868, 1641, 1456, 1418, 1360, 1329, 1119, 1066 cm^{-1}. **HRMS-ESI**: calculated for ($C_{21}H_{39}NO_3S$+Na) 408.2543, found 408.2561.



70

To a solution of acetal **70** (91 mg, 0.236 mmol) in THF (1.0 mL) was added 10% oxalic acid (0.60 mL). The mixture was stirred at rt for 1h, and then quenched with Na_2CO_3 (aq) and extracted with diethyl ether. The organic extract was dried over Na_2SO_4 and concentrated. Purification by flash column chromatography with diethyl ether

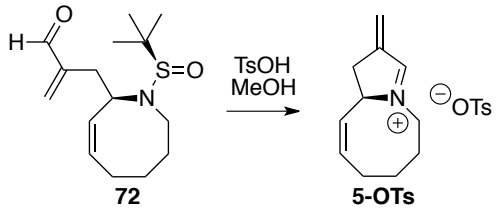
afforded the aldehyde as colorless oil (69 mg, 0.221 mmol, 94%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.40 (s, 1H), 6.28 (s, 1H), 6.00 (s, 1H), 5.66 (m, 2H), 5.02 (d, *J* = 10.6 Hz, 1H), 4.96 (d, *J* = 17.0 Hz, 1H), 4.91 (app d, *J* = 17.0 Hz, 1H), 4.86 (d, *J* = 10.0 Hz, 1H), 3.87 (bs, 1H), 3.07 (m, 1H), 2.71 (m, 1H), 2.65 (m, 1H), 2.58 (m, 1H), 1.97 (m, 2H), 1.53 (m, 1H), 1.42 (m, 1H), 1.28 (m, 2H), 1.08 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.0, 146.5, 138.1, 137.0, 136.3, 116.8, 114.6, 60.1, 57.7, 43.5, 33.1, 31.2, 29.5, 26.2, 23.4. **$[\alpha]^{23}_D$** = +48.5 (*c* 2.10, $CHCl_3$). **IR** (film): 3079, 2978, 2932, 2864, 1689, 1640, 1458, 1419, 1361, 1063 cm^{-1}. **HRMS-ESI**: calculated for ($C_{17}H_{29}NO_2S$+Na) 334.1811, found 334.1807.



72

A solution of olefin (46 mg, 0.148 mmol) in toluene (140 mL) was heated in a 110 °C oil bath. Hoveyda-Grubbs 2nd generation catalyst (20 mg) in toluene (1.0 mL) was added in 4 portions over 2 hours. After another 30 min, the solution was cooled and filtered through silica gel and eluted with DCM, then EtOAc to obtain product **72** (28 mg, 0.097 mmol, 67%). Recrystallization from diethyl ether afforded analytical pure compound. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.53 (s, 1H), 6.39 (s, 1H), 6.13 (s, 1H), 5.66 (m, 1H), 5.21 (ddd, J = 11.5, 6.4, 1.8 Hz, 1H), 4.34 (m, 1H), 3.46 (ddd, J = 12.8, 10.5, 1.8 Hz, 1H), 3.20 (ddd, J = 14.2, 6.4, 1.8 Hz, 1H), 2.82 (dd, J = 13.7, 5.0 Hz, 1H), 2.74 (m, 1H), 2.59 (dd, J = 13.7, 10.1 Hz, 1H), 2.00 (ddd, J = 17.9, 8.7, 4.6 Hz, 1H), 1.92 (m, 1H), 1.72 (m, 1H), 1.59 (m, 1H), 1.37 (m, 1H), 1.19 (s, 9H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 194.2, 147.1, 136.3, 130.1, 129.7, 58.3, 56.0, 43.9, 32.2, 26.7, 26.5, 24.6, 23.8. **$[\alpha]^{23}_D$** = −19.9 (*c* 0.34, $CHCl_3$).

IR (film): 3053, 2984, 2928, 2861, 1691, 1445, 1421, 1362 cm^{-1}. **HRMS-ESI**: calculated for ($C_{15}H_{25}NO_2S$+K) 322.1238, found 322.1236.

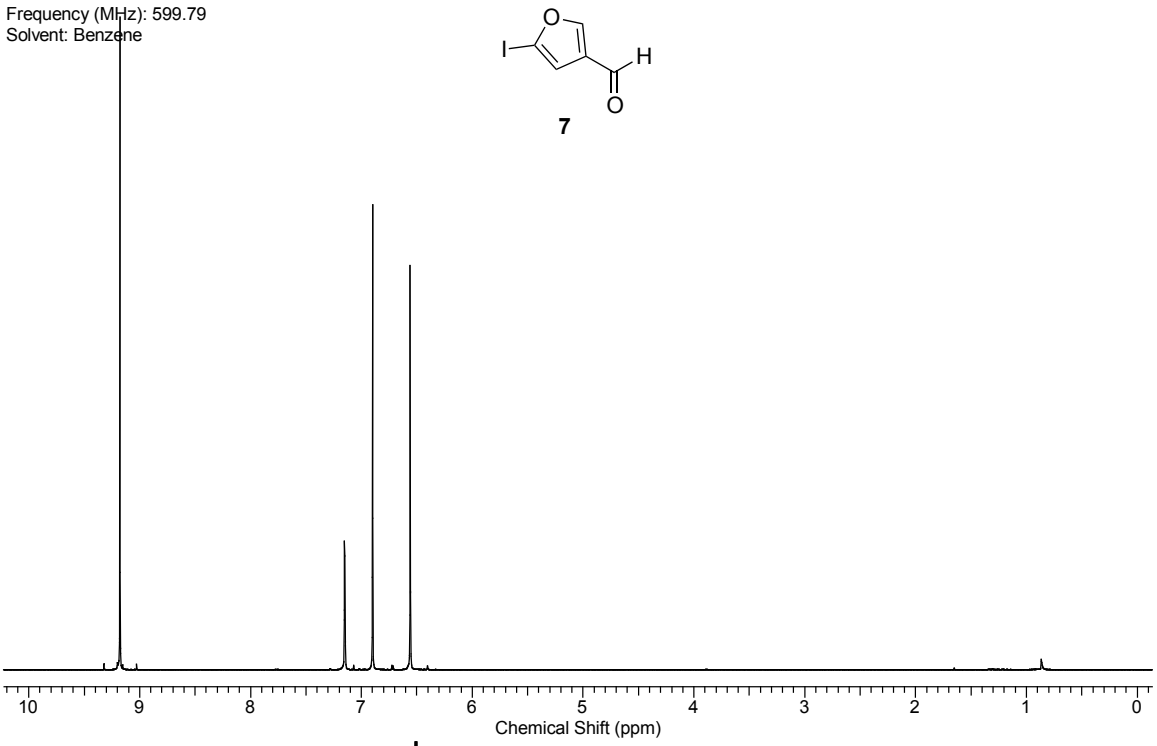


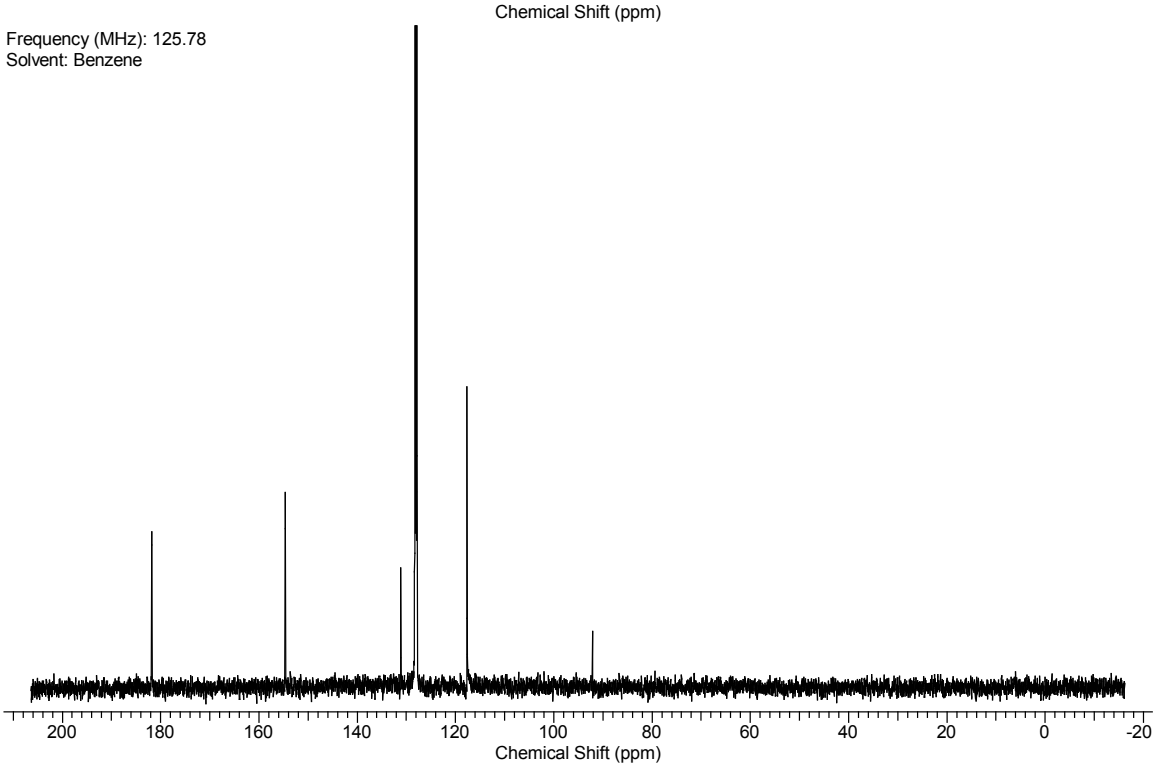
72 **5-OTs**

A mixture of aldehyde **72** (8.8 mg, 0.031 mol) and TsOH•H_2O (6.3 mg, 0.033 mmol) in MeOH (0.30 mL) was stirred at rt for 2h. The solvent was removed and the residue was dissolved in $CHCl_3$ (0.30 mL). The solution was stirred at 40 °C for 6h and concentrated. The residue was washed with diethyl ether and decanted, dried under high vacuum afforded iminium **5-OTs** (10.9 mg, 0.032 mmol, quant.). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.46 (s, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.44 (bs, 1H), 6.11 (m, 1H), 6.01 (bs, 1H), 5.41 (m, 2H), 4.46 (m, 1H), 3.96 (m, 1H), 3.35 (m, 1H), 2.70 (m, 1H), 2.31 (s, 3H), 2.25 (m, 2H), 2.00 (m, 2H), 1.81 (m, 1H), 1.46 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.4, 143.0, 142.9, 139.5, 139.1, 131.1, 128.6, 125.9, 125.6, 66.2, 52.8, 33.9, 27.2, 26.4, 26.2, 21.2. **$[\alpha]^{23}_D$** = −102 (*c* 0.80, $CHCl_3$). **IR** (film): 3427, 3007, 2946, 2864, 1621, 1496, 1445, 1215, 1182, 1123 cm^{-1}. **HRMS-ESI**: calculated for ($C_{11}H_{16}N$) 162.1277, found 162.1244.

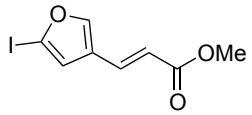
Appendix I

Chapter Two NMR Spectra


Frequency (MHz): 599.79
Solvent: Benzene
O
I
H
O
7
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

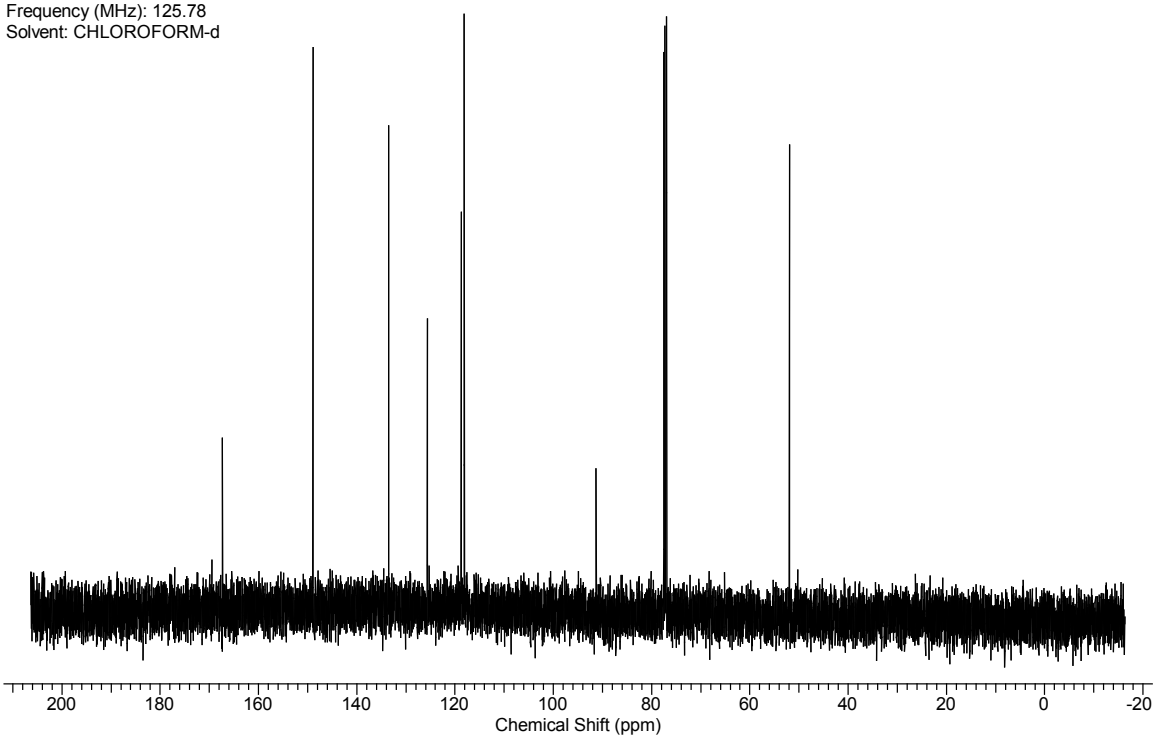

Frequency (MHz): 125.78
Solvent: Benzene
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

Frequency (MHz): 500.18
Solvent: CHLOROFORM-d

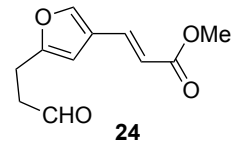


23

Frequency (MHz): 125.78
Solvent: CHLOROFORM-d

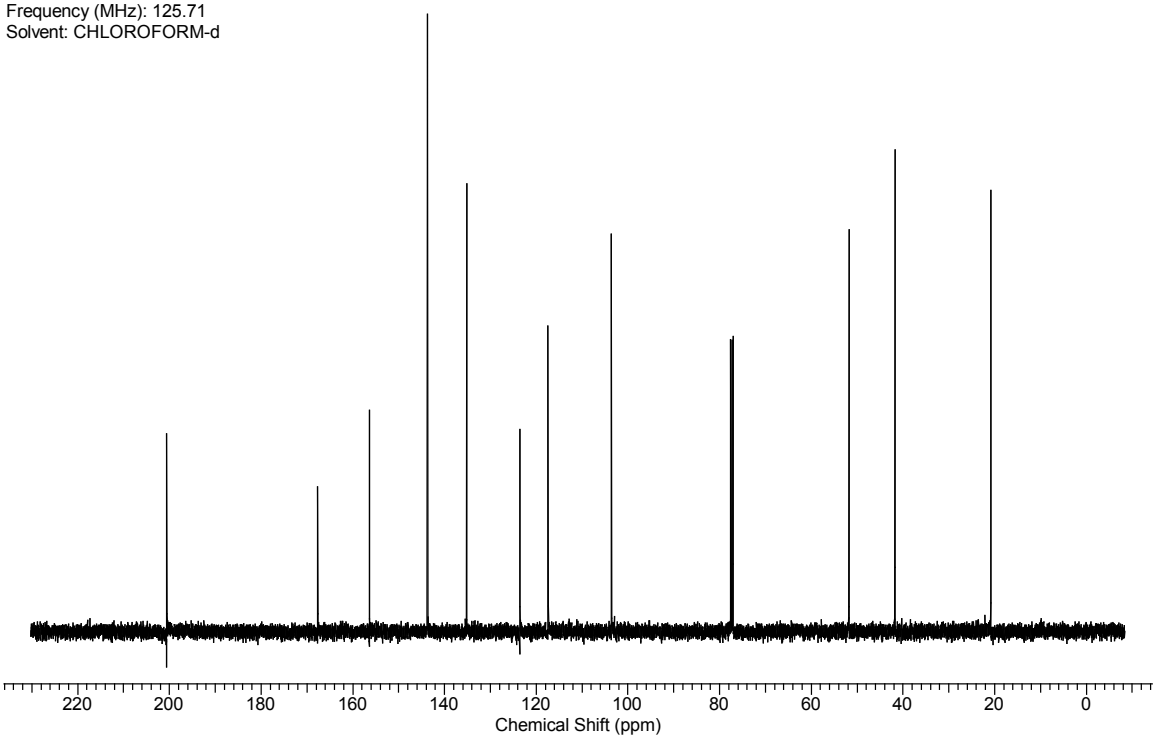


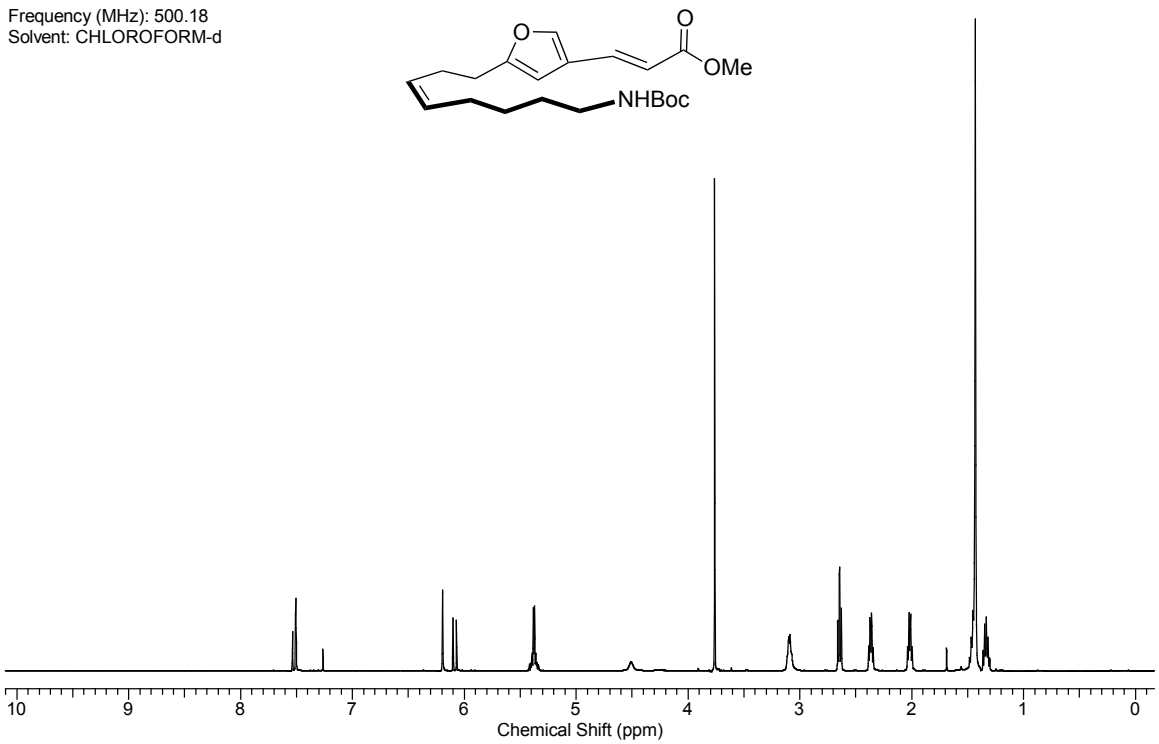
Frequency (MHz): 499.87
Solvent: CHLOROFORM-d

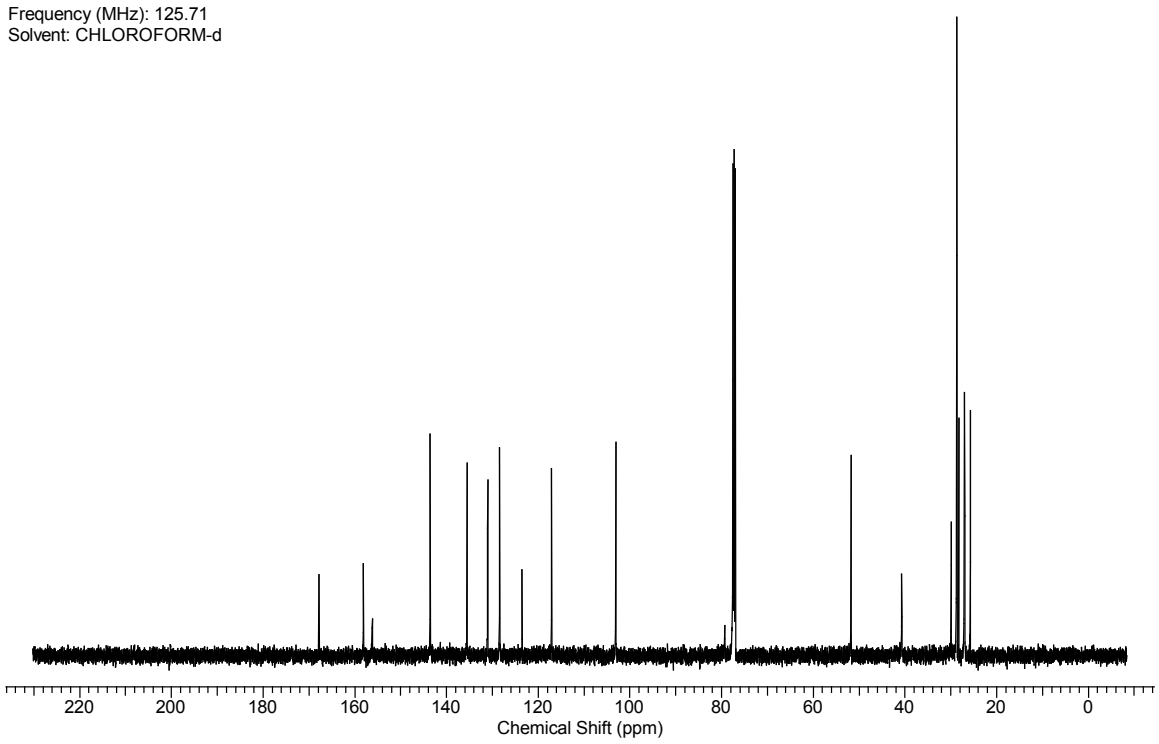


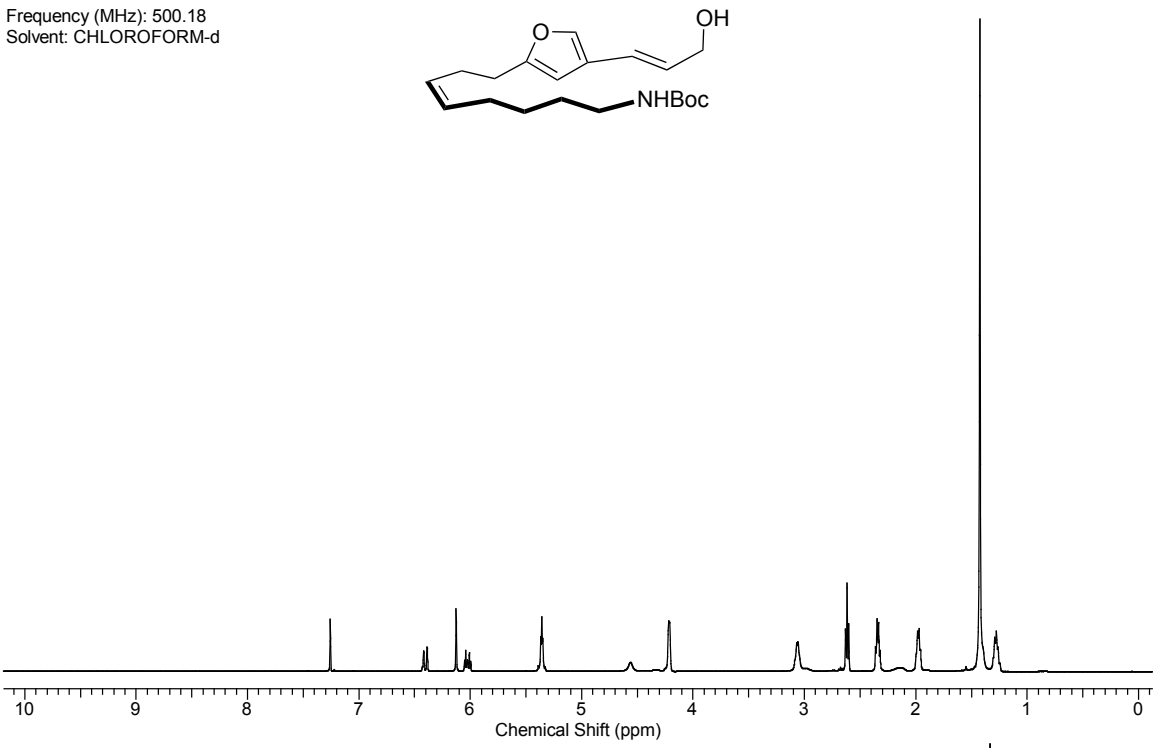
24

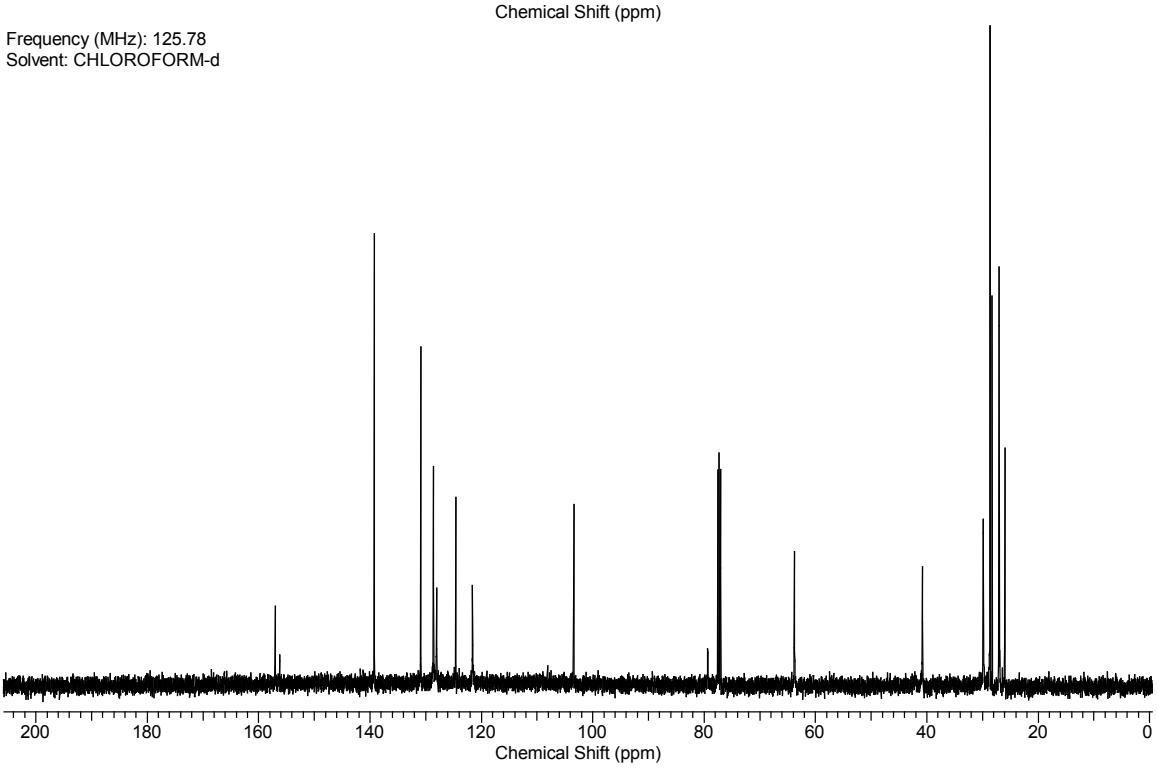
Frequency (MHz): 125.71
Solvent: CHLOROFORM-d

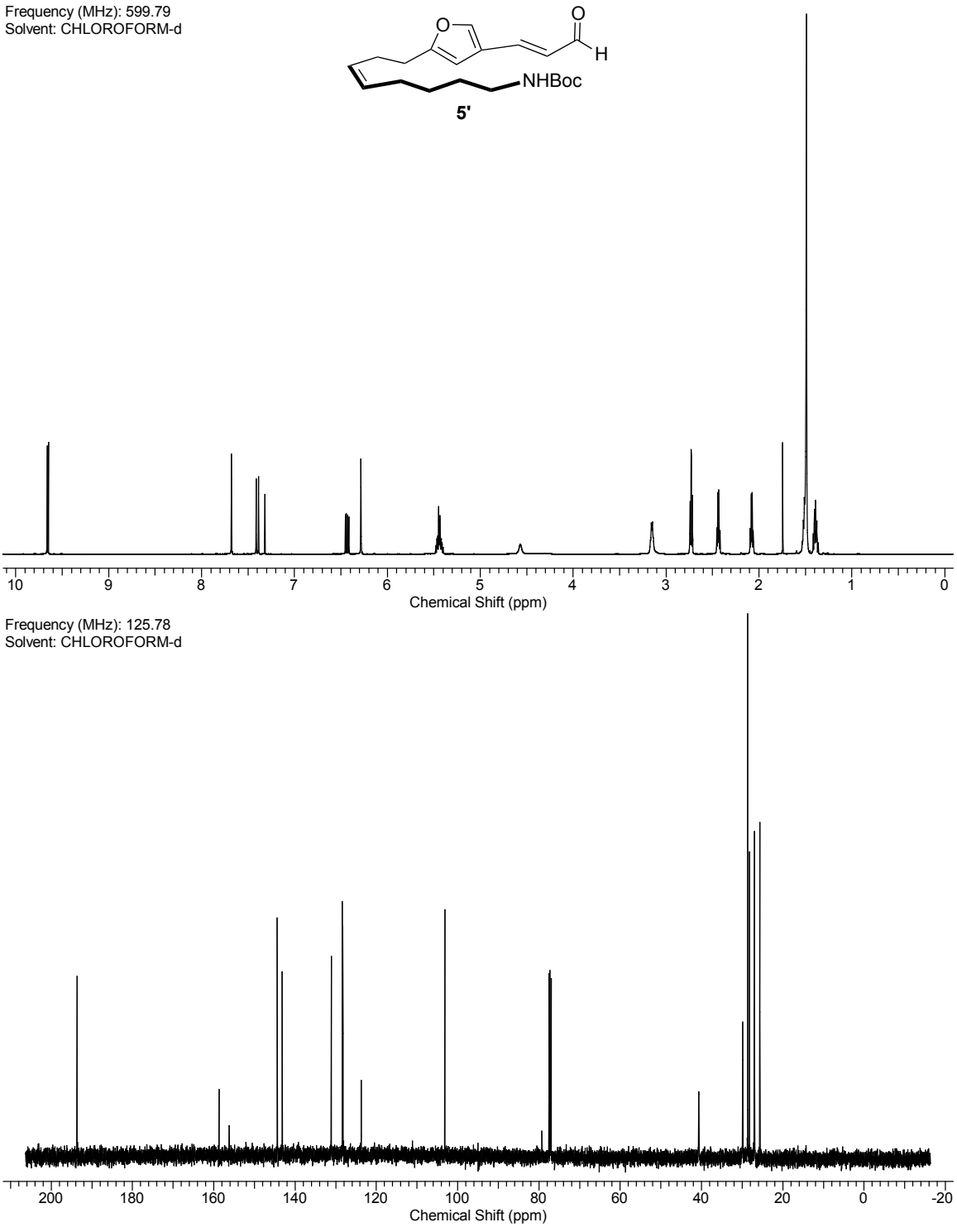


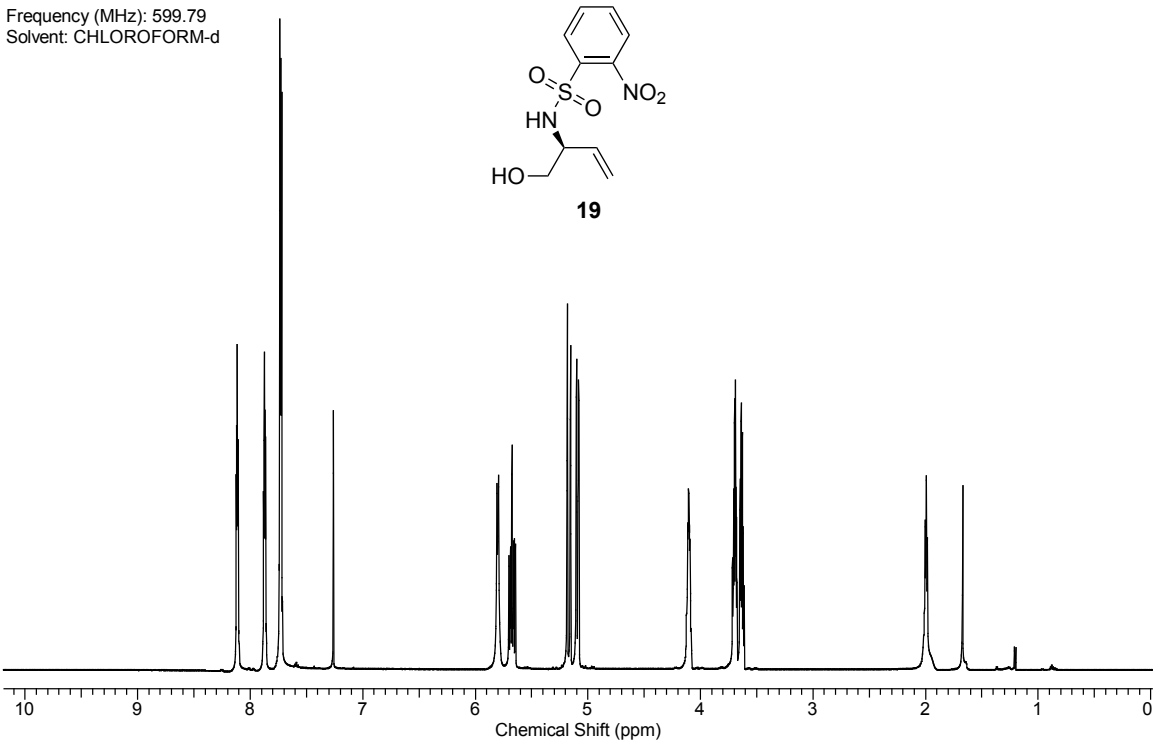

Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
O
O
OMe
NHBoc
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

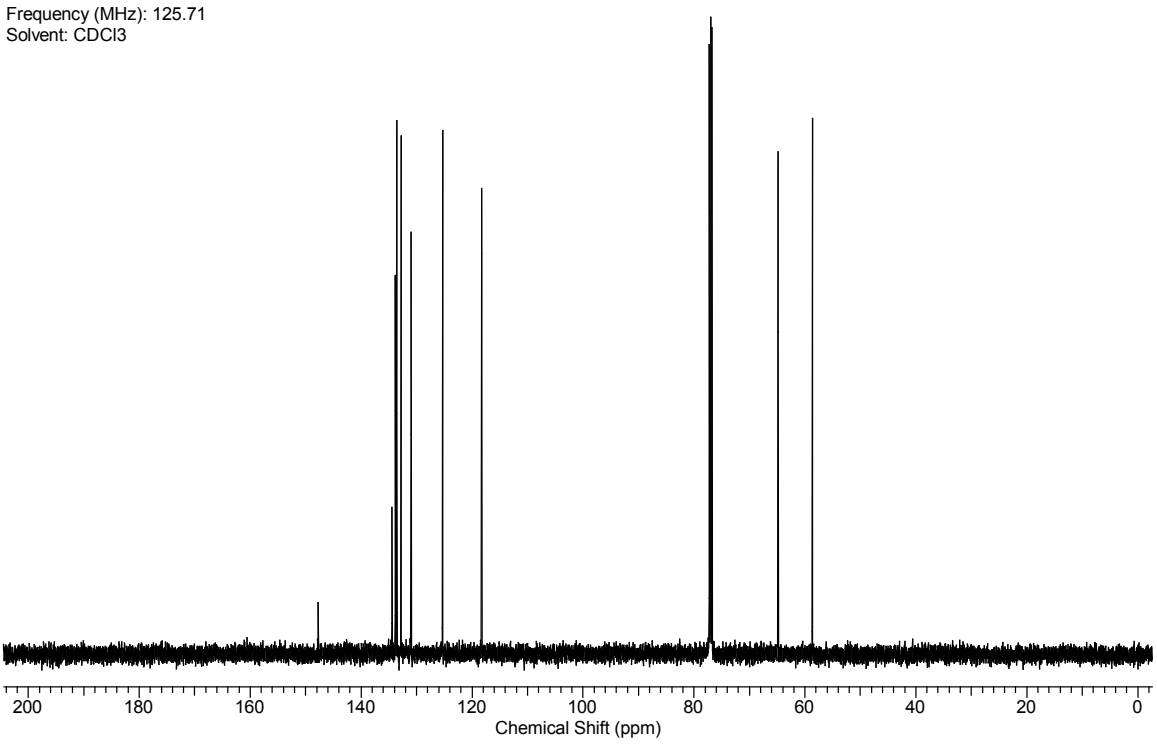

Frequency (MHz): 125.71
Solvent: CHLOROFORM-d
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

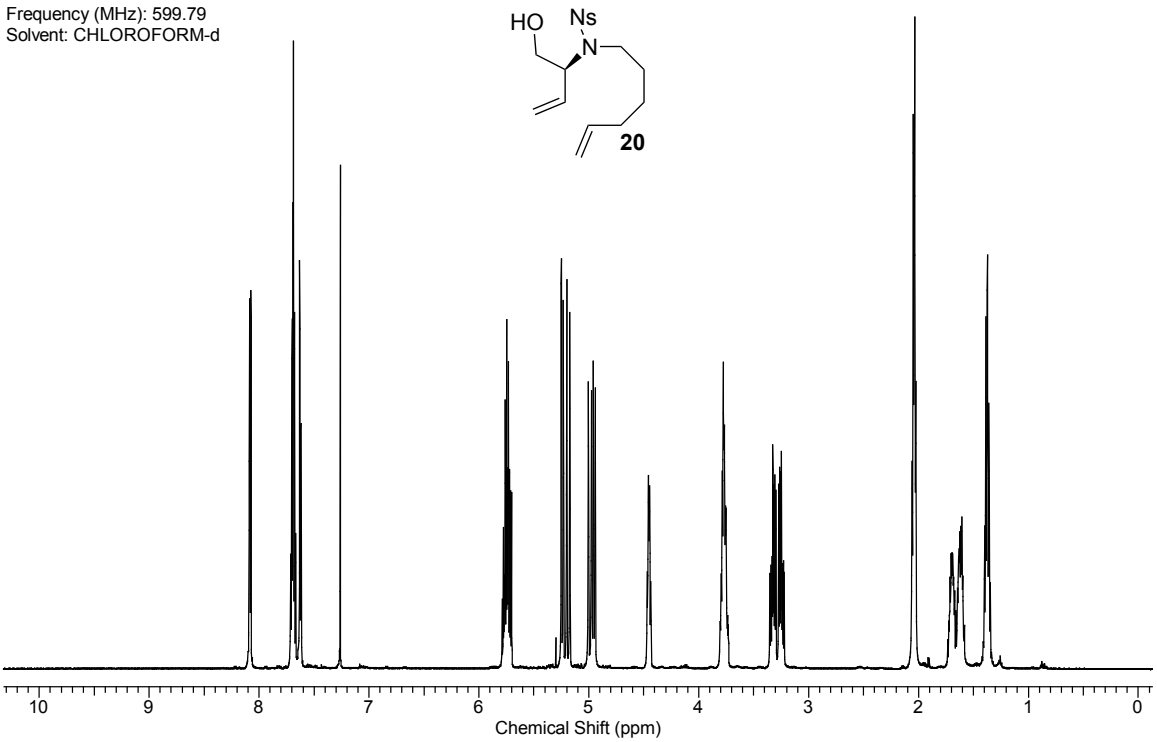

Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
O
OH
NHBoc
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

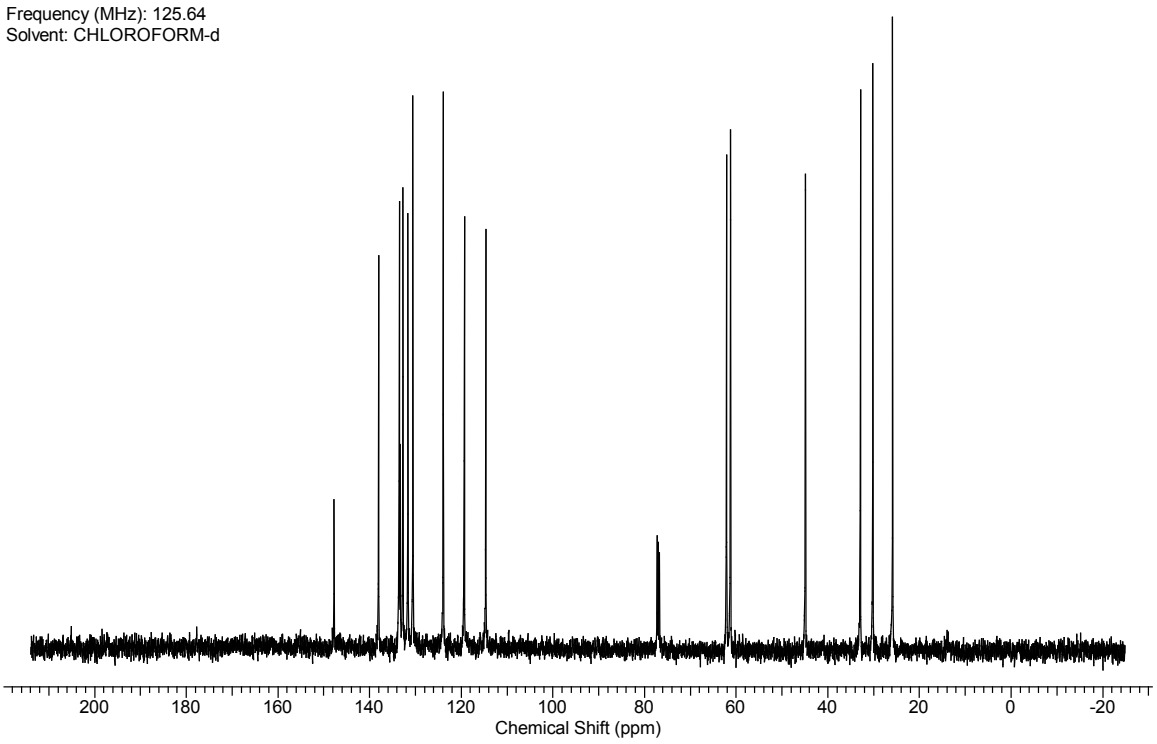

Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

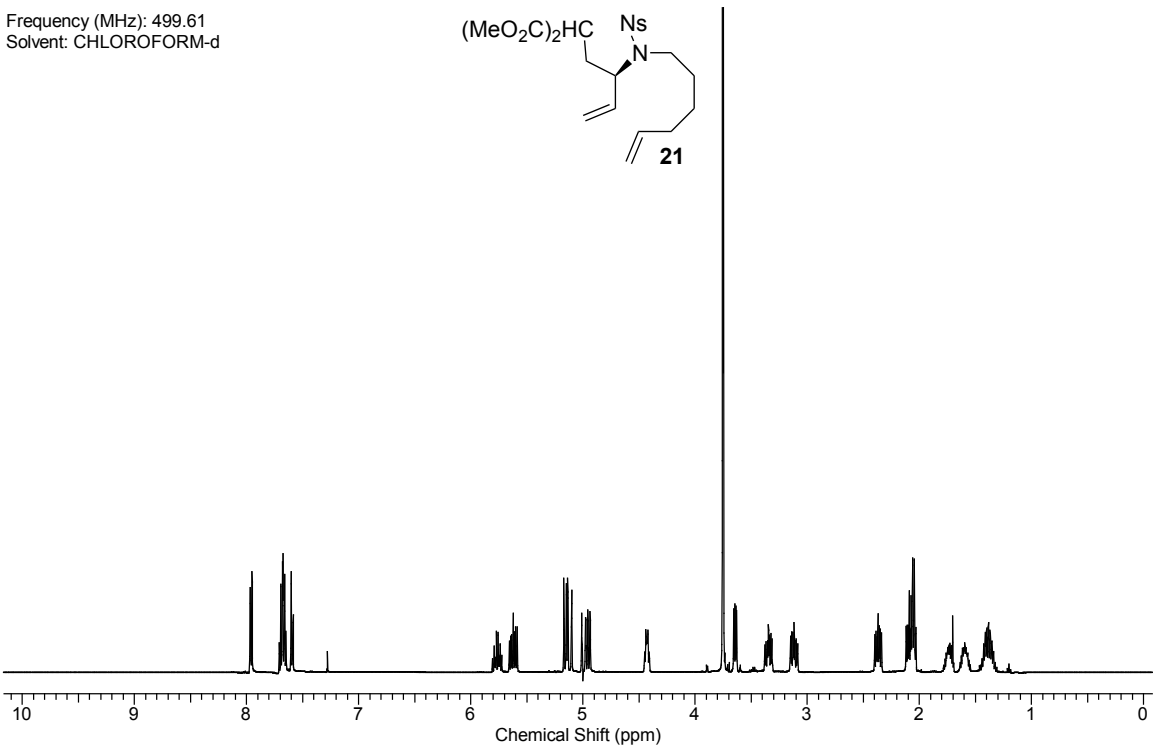

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
O
O
H
NHBoc
5'
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

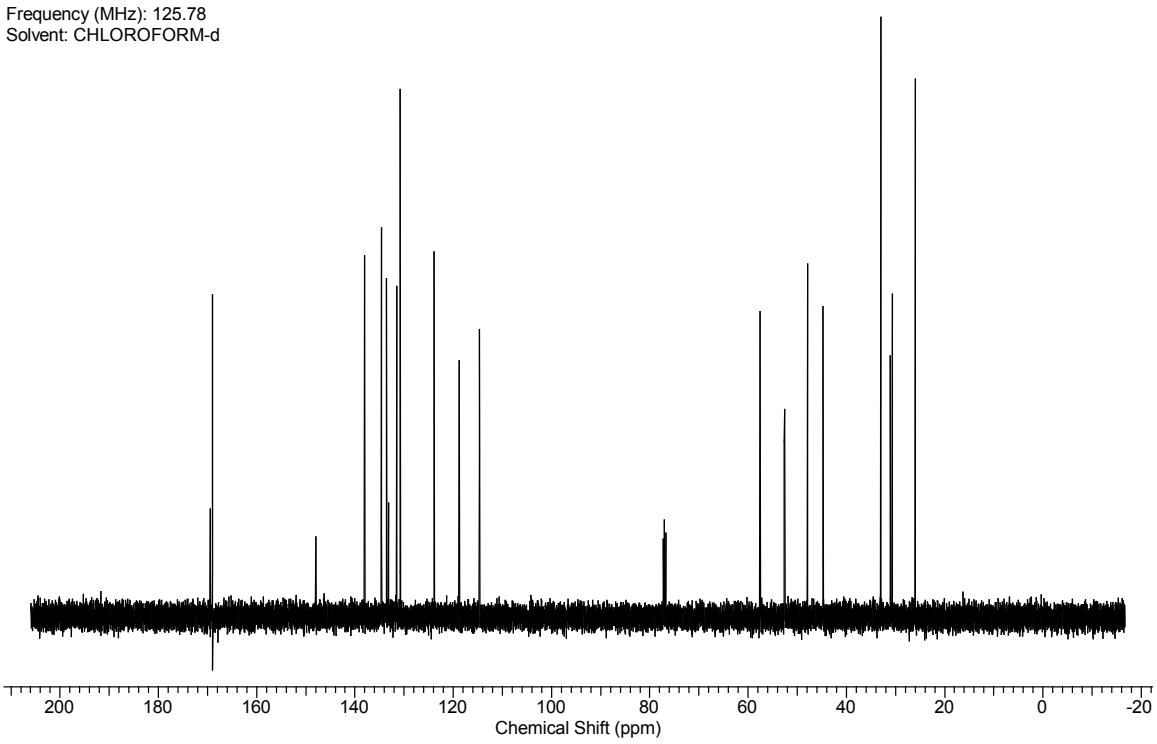

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
O
S
O
NO2
HN
HO
19
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

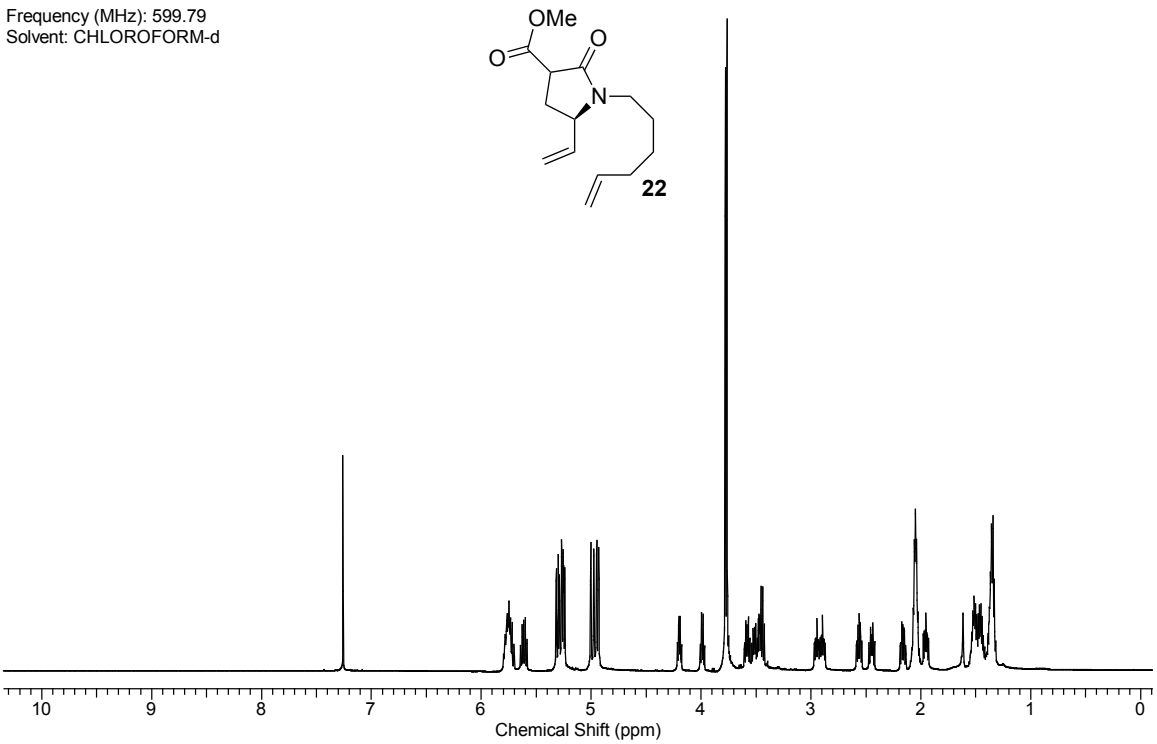

Frequency (MHz): 125.71
Solvent: CDCl3
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

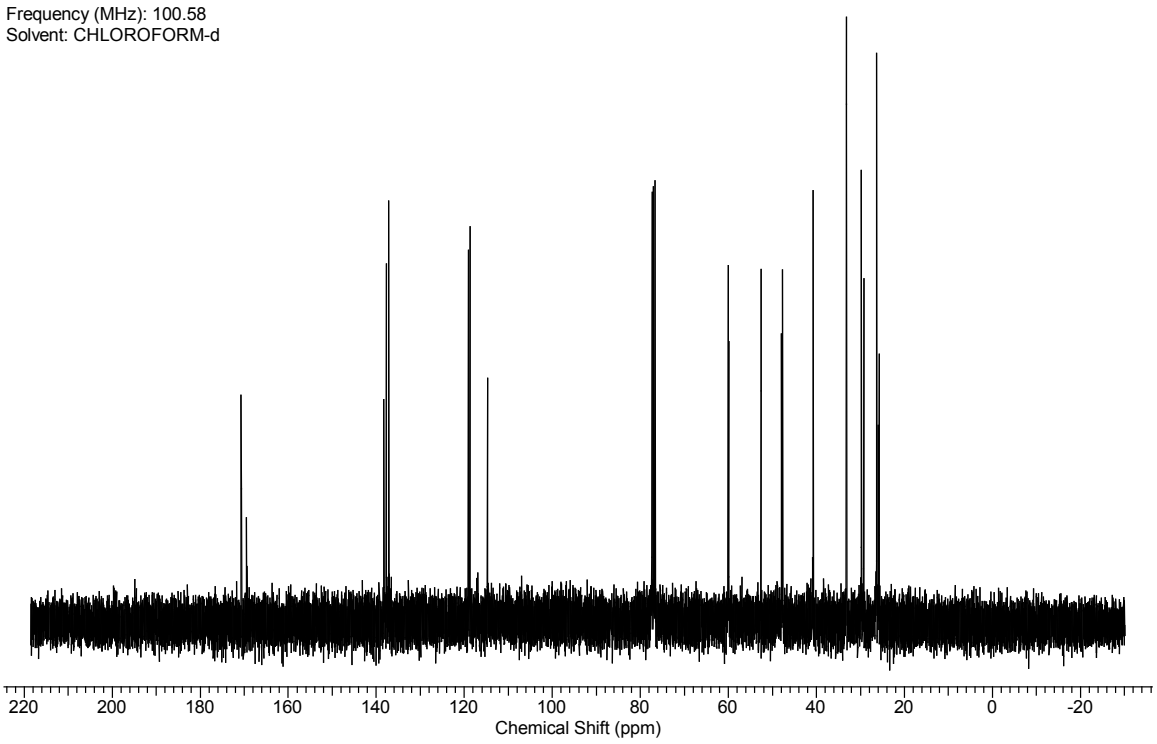

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
HO
Ns
N
20
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

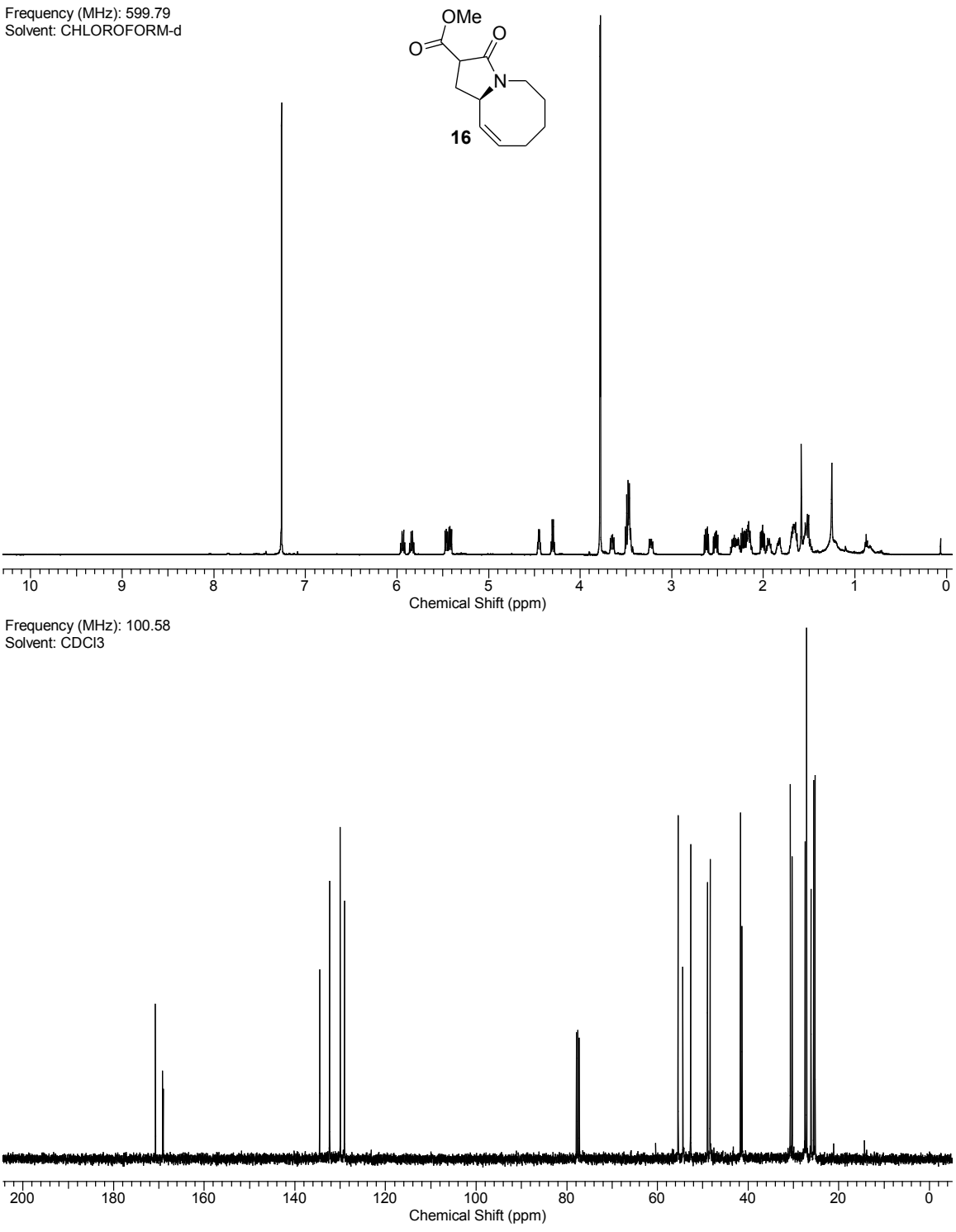

Frequency (MHz): 125.64
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

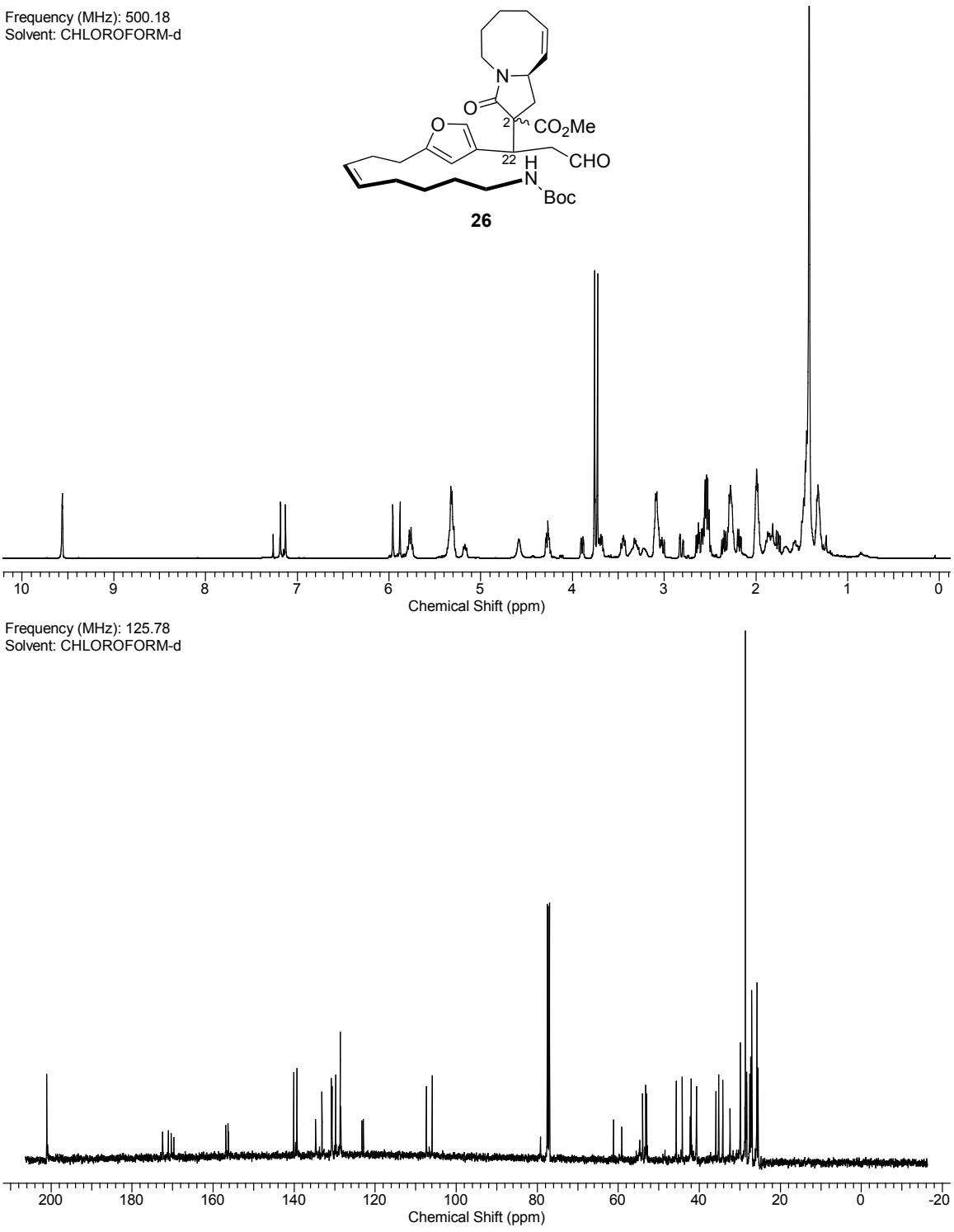

Frequency (MHz): 499.61
Solvent: CHLOROFORM-d
(MeO2C)2HC
Ns
N
21
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

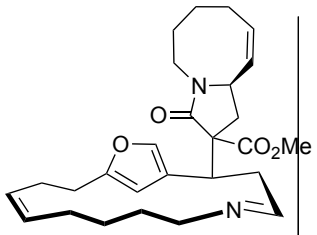

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
OMe
O
O
N
22
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 100.58
Solvent: CHLOROFORM-d
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

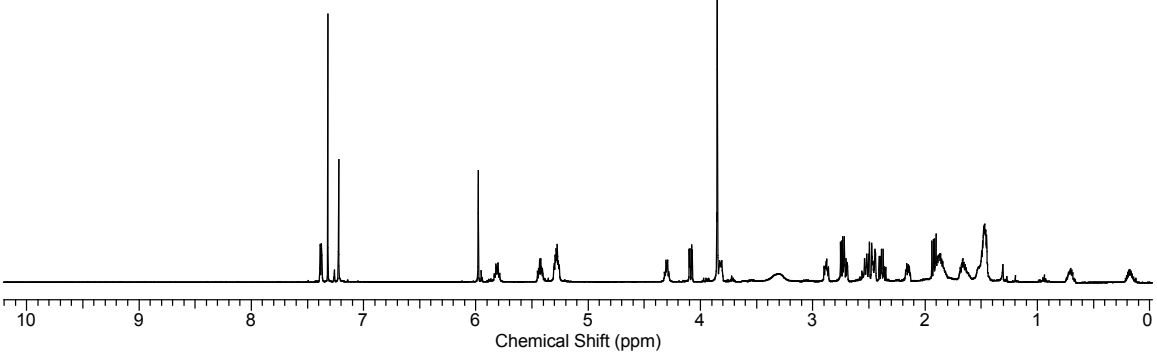

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
OMe
O
O
N
16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
Frequency (MHz): 100.58
Solvent: CDCl3
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
N
O
2
CO2Me
O
22
H
CHO
N
Boc
26
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

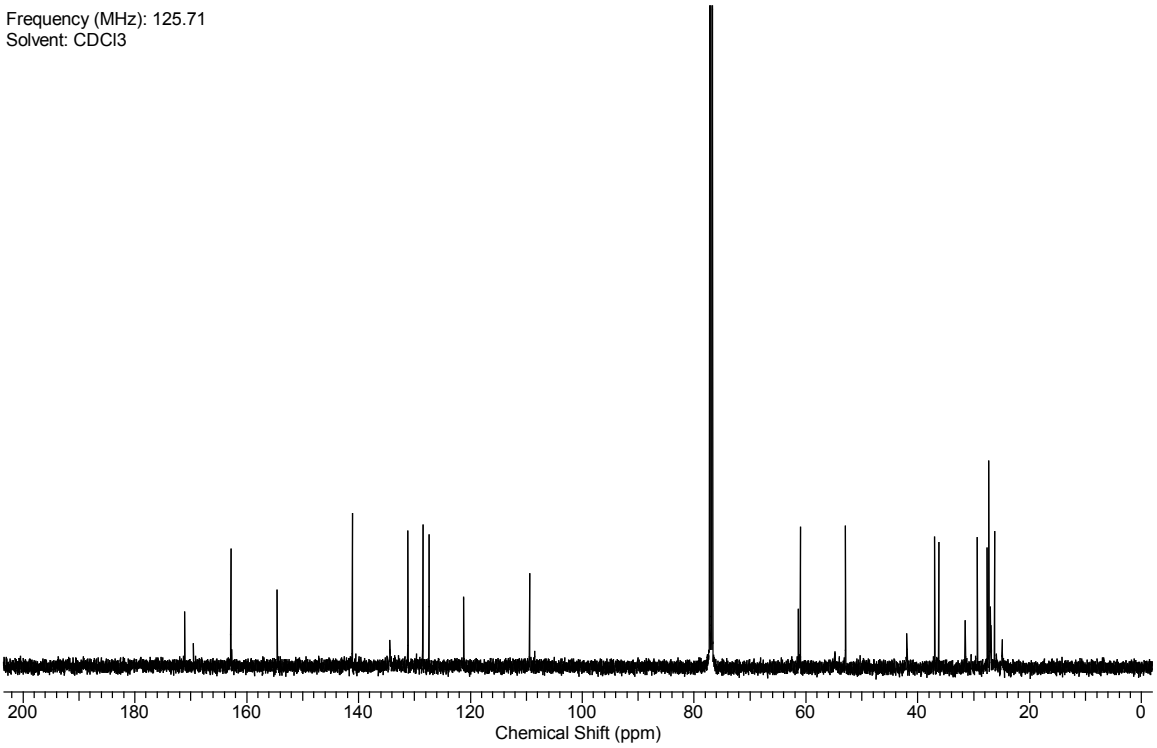
Frequency (MHz): 599.79
Solvent: CHLOROFORM-d



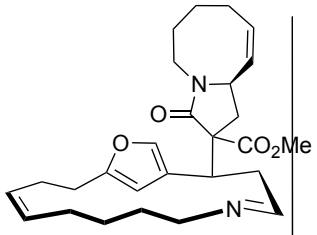
27 (less polar diastereomer)



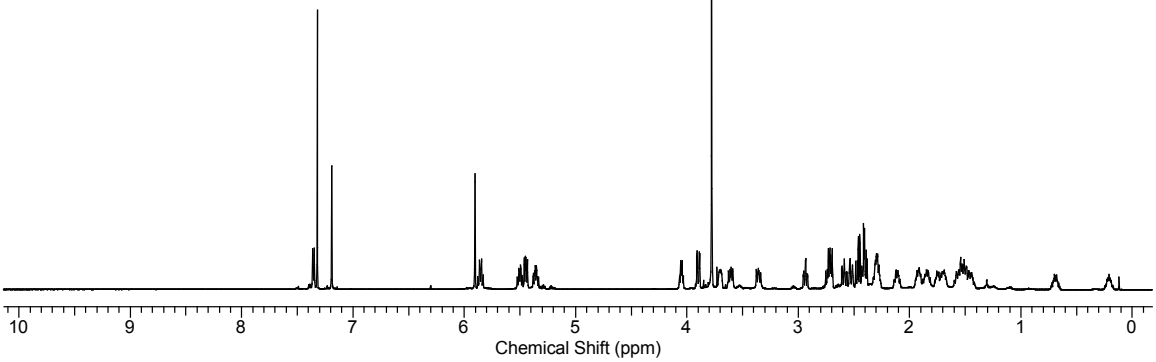
Frequency (MHz): 125.71
Solvent: CDCl3



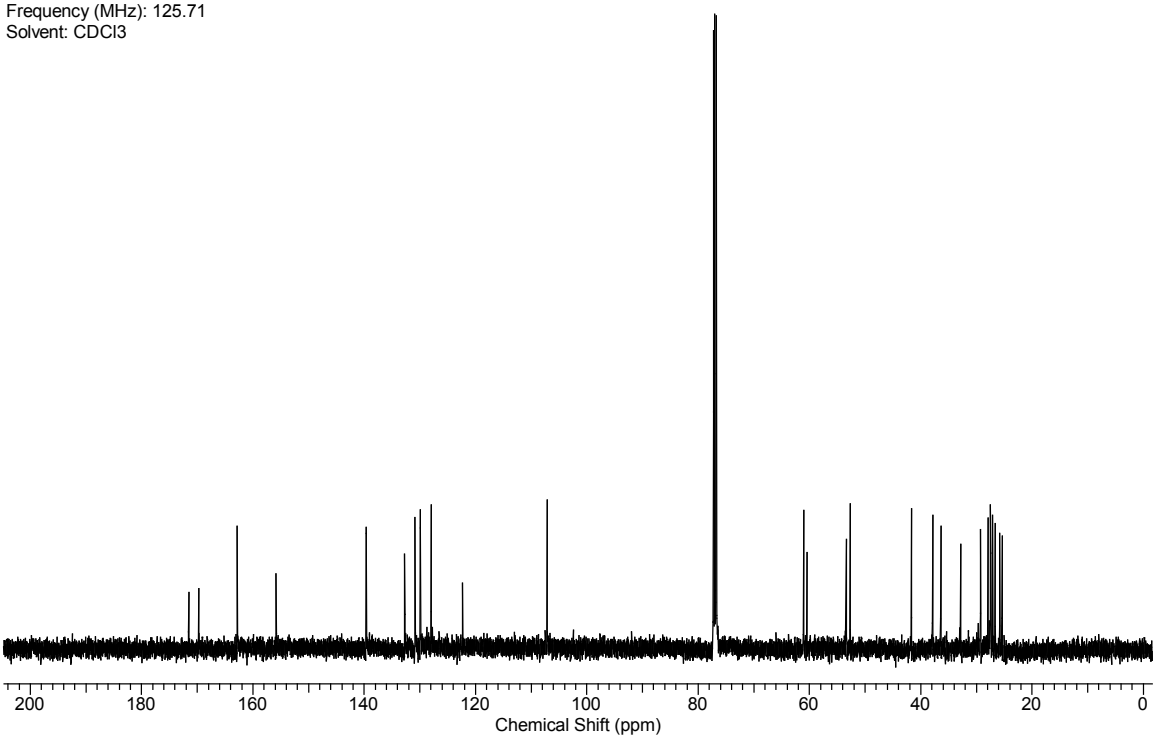
Frequency (MHz): 599.79
Solvent: CHLOROFORM-d

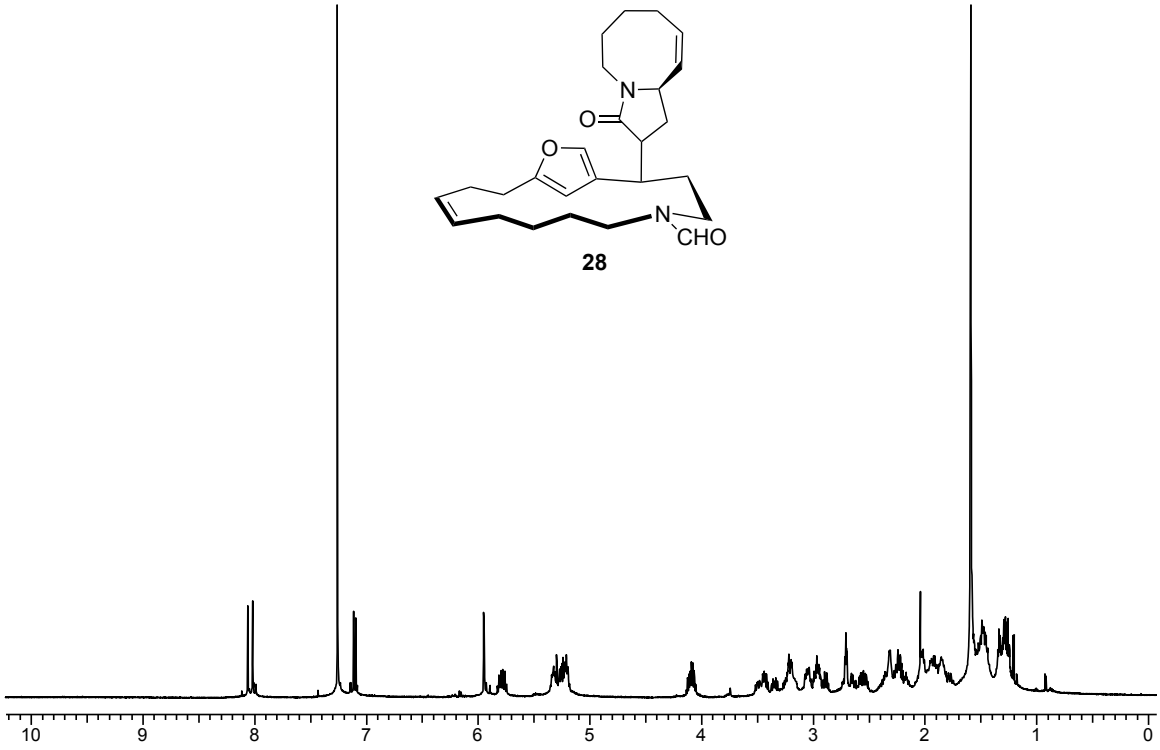


27 (more polar diastereomer)



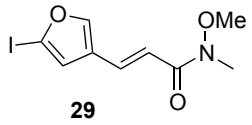
Frequency (MHz): 125.71
Solvent: CDCl3



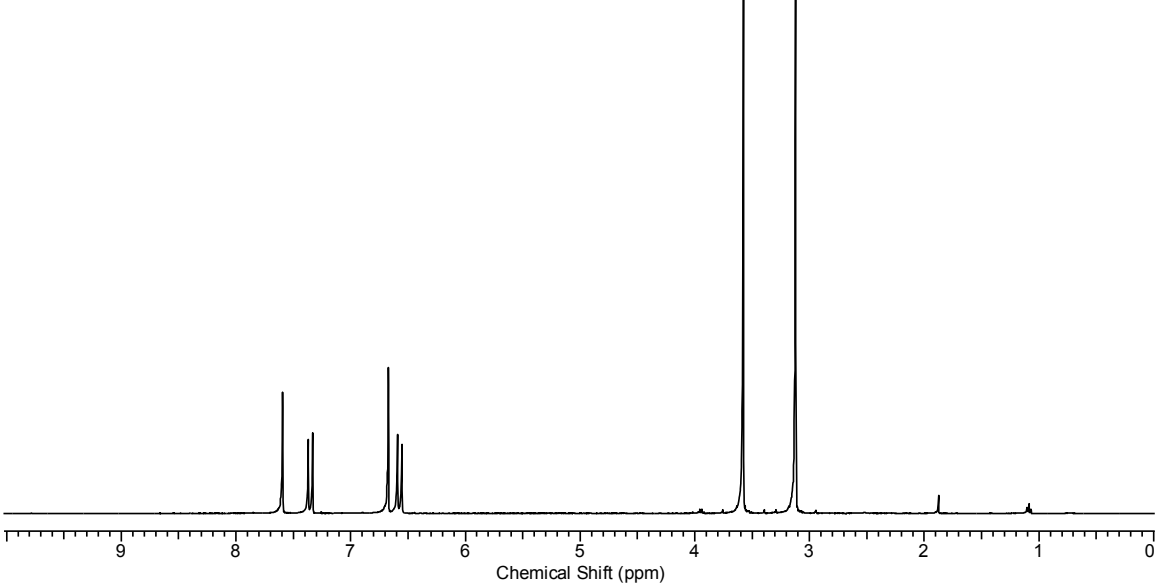


28

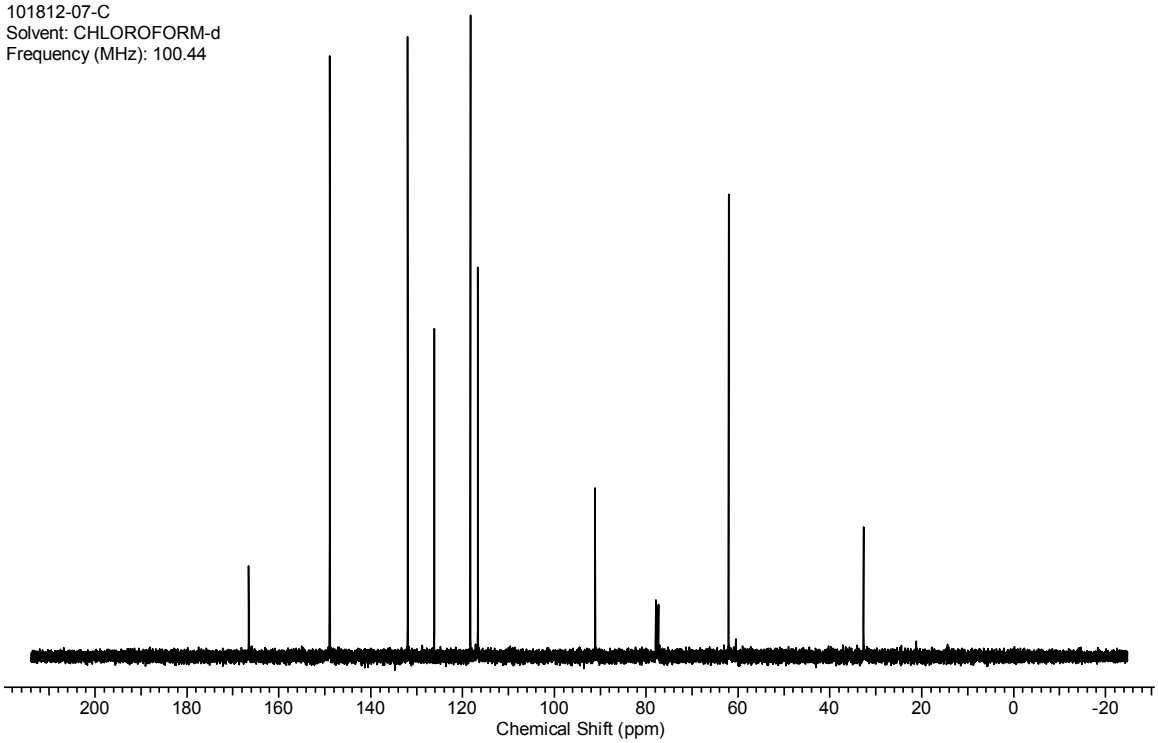
101812-07
Solvent: CHLOROFORM-d
Frequency (MHz): 399.41



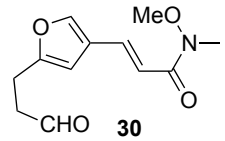
29



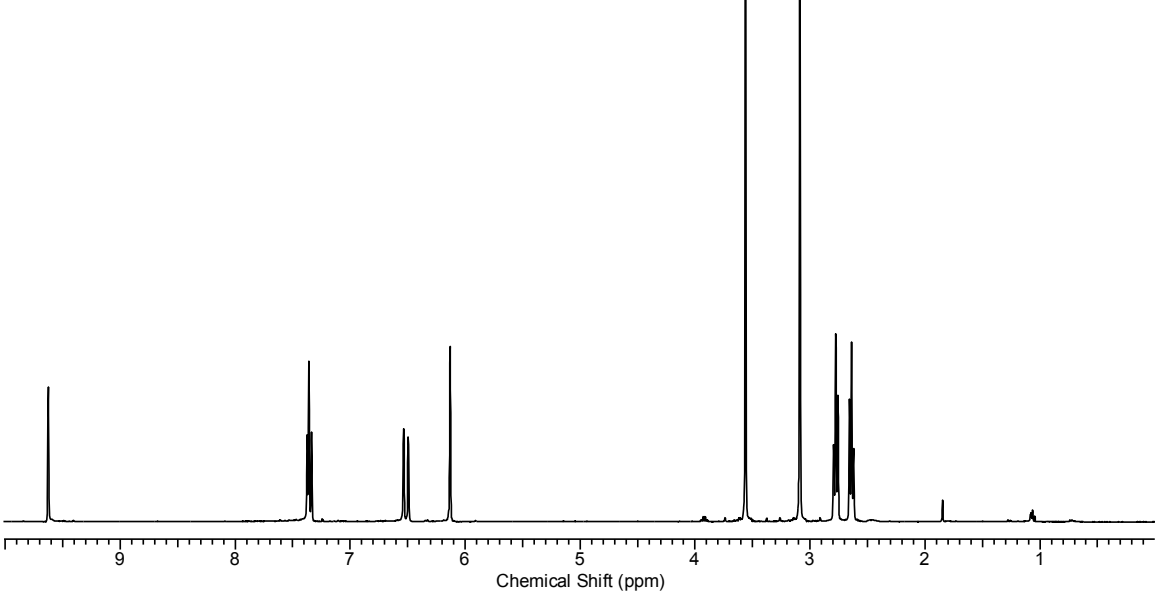
101812-07-C
Solvent: CHLOROFORM-d
Frequency (MHz): 100.44



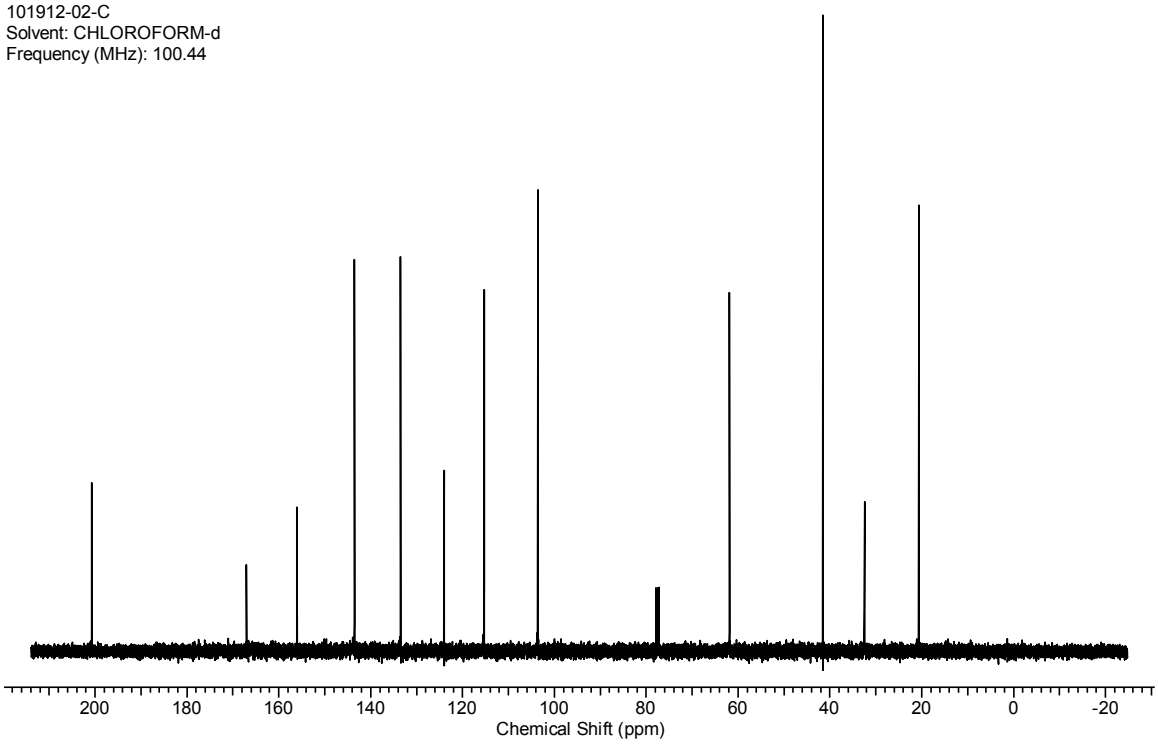
101912-02
Solvent: CHLOROFORM-d
Frequency (MHz): 399.41

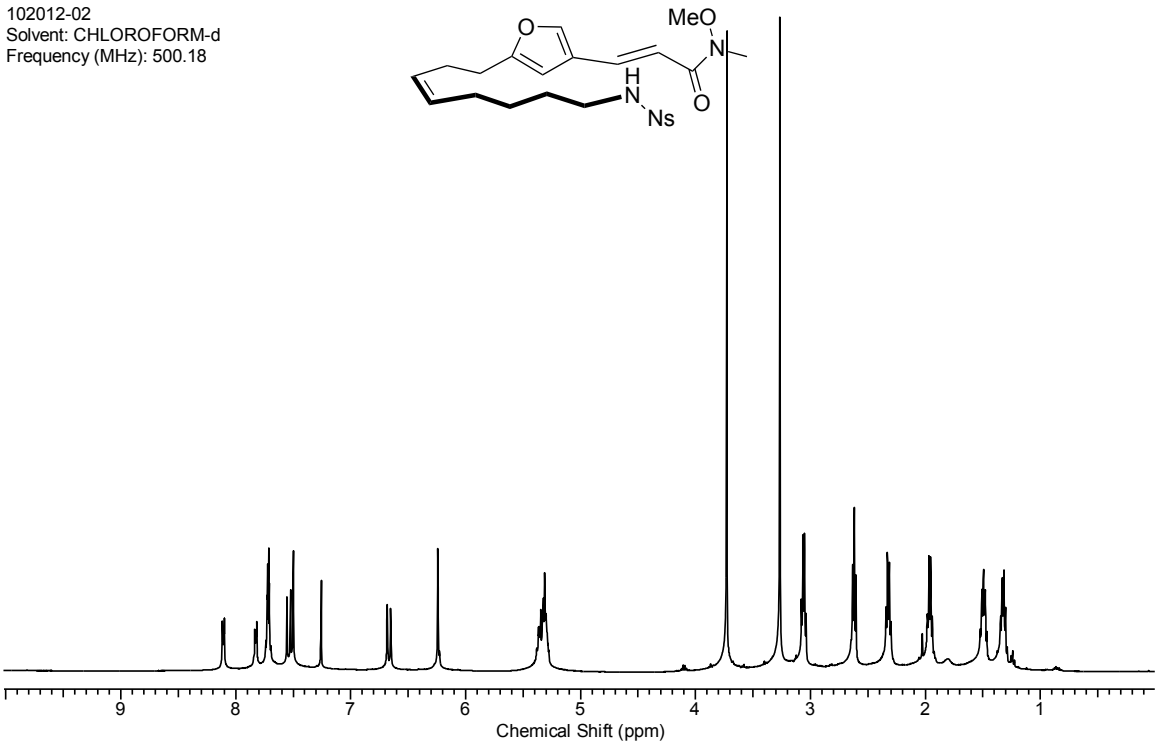


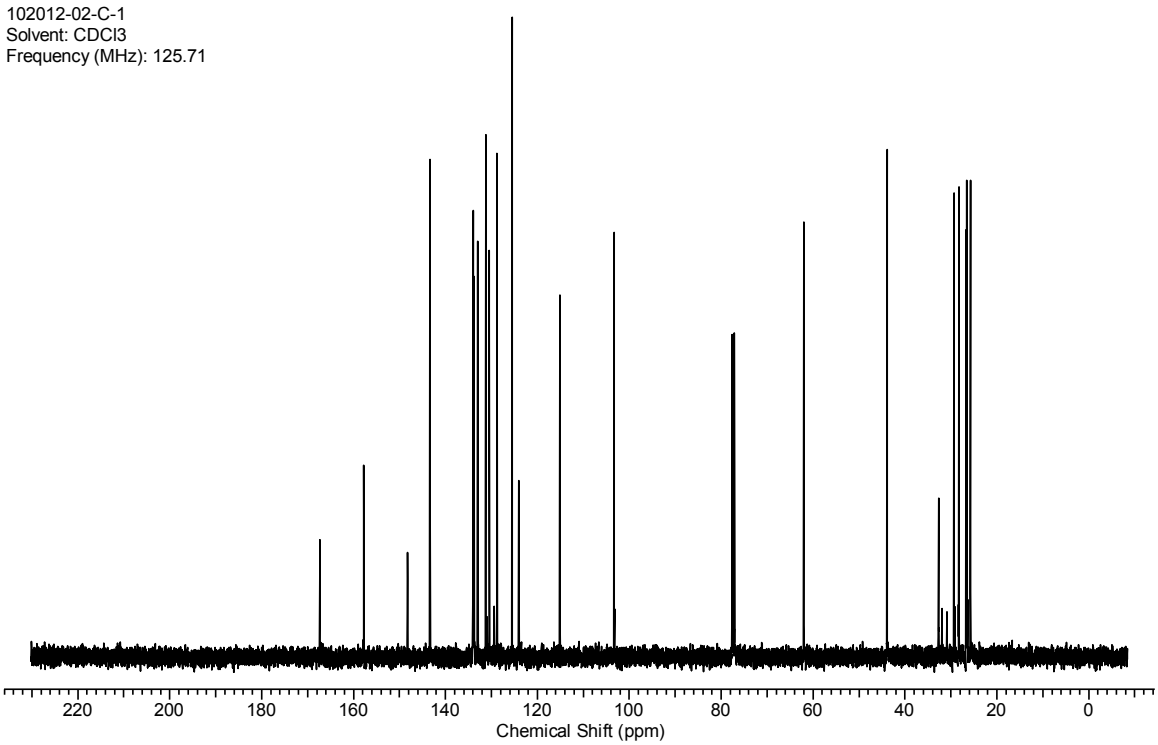
30

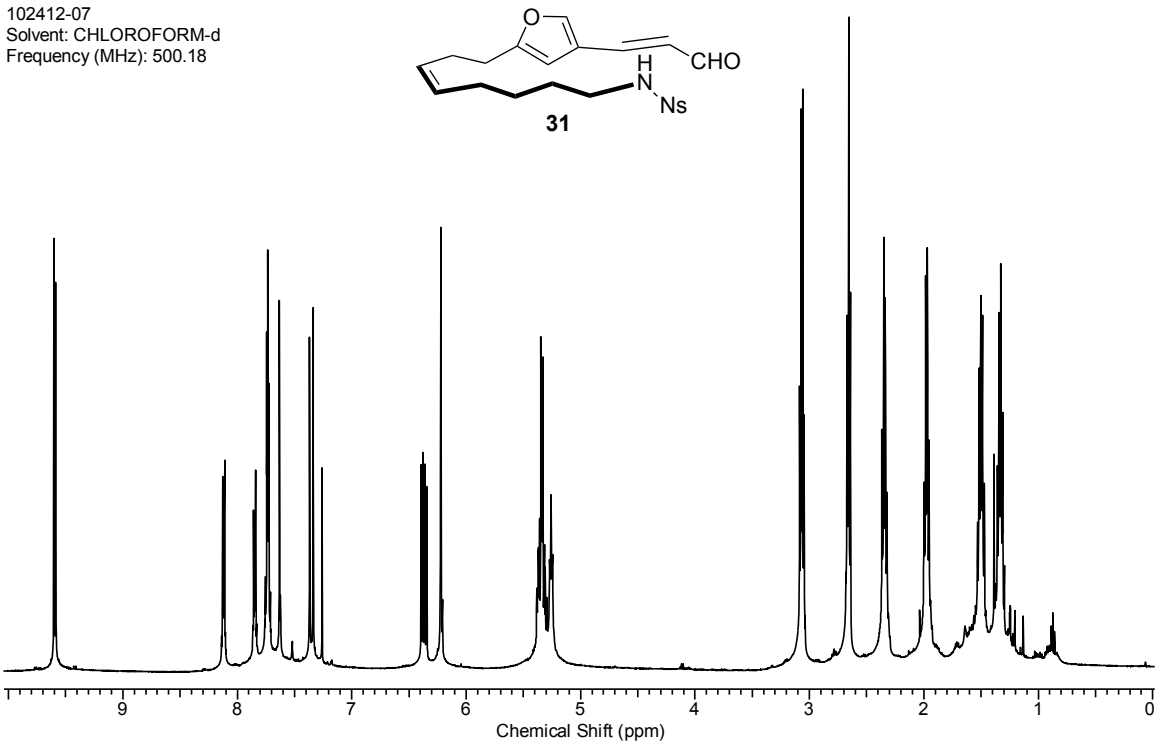


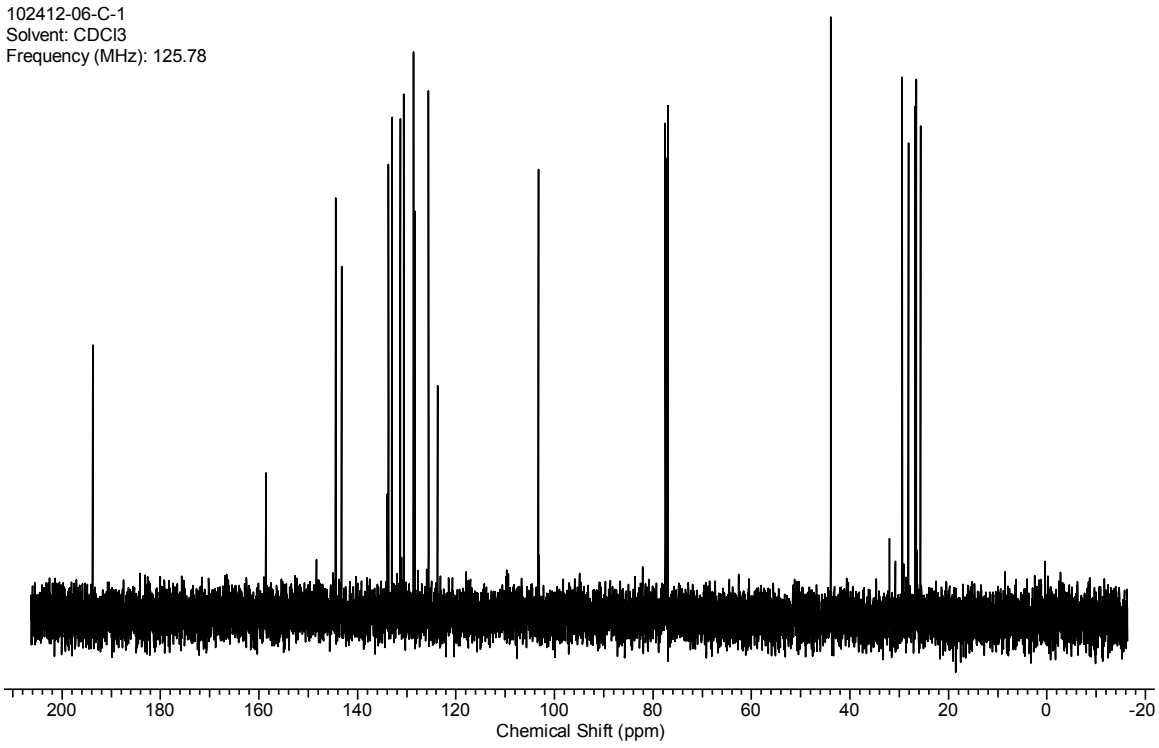
101912-02-C
Solvent: CHLOROFORM-d
Frequency (MHz): 100.44



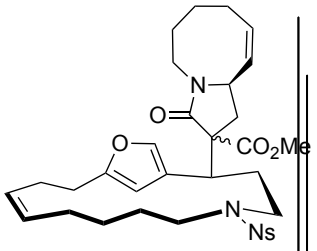

102012-02
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18
O
MeO
N
H
N
Ns
O
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

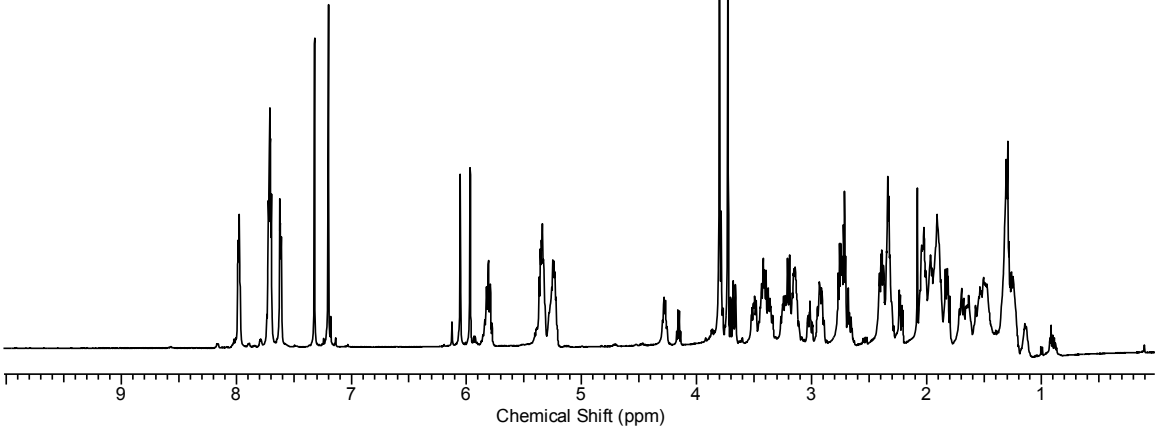

102012-02-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


102412-07
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18
O
CHO
H
N
Ns
31
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

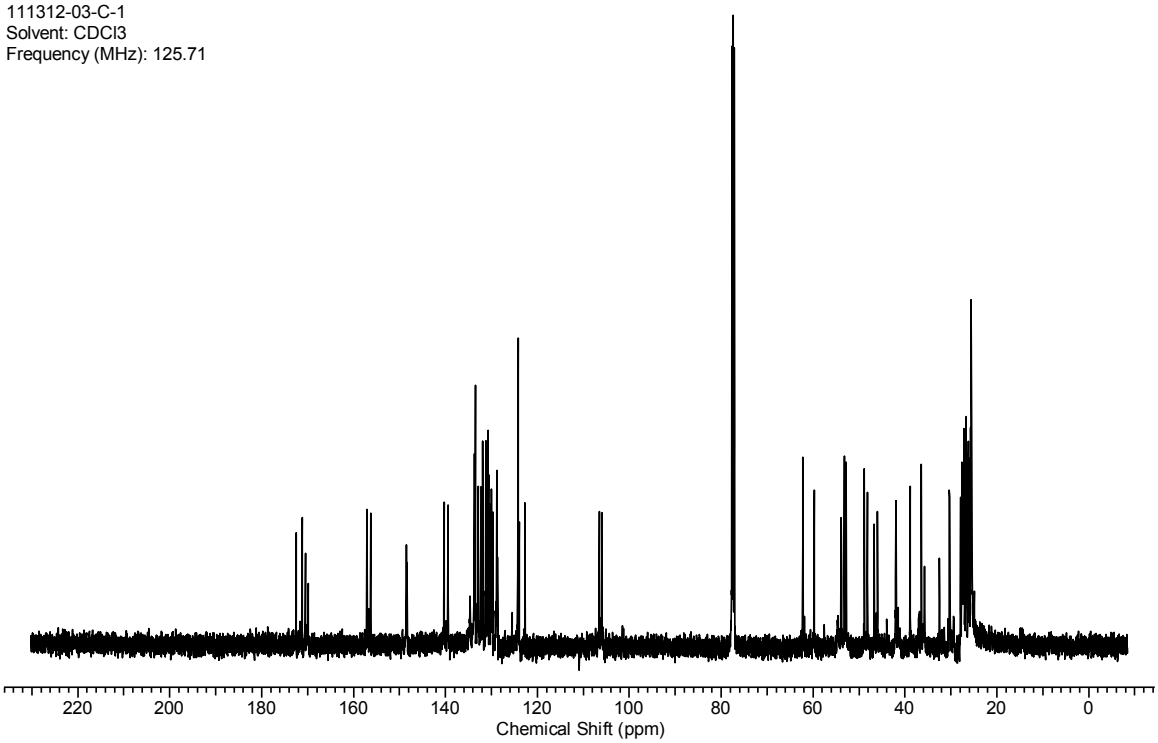

102412-06-C-1
Solvent: CDCl3
Frequency (MHz): 125.78
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

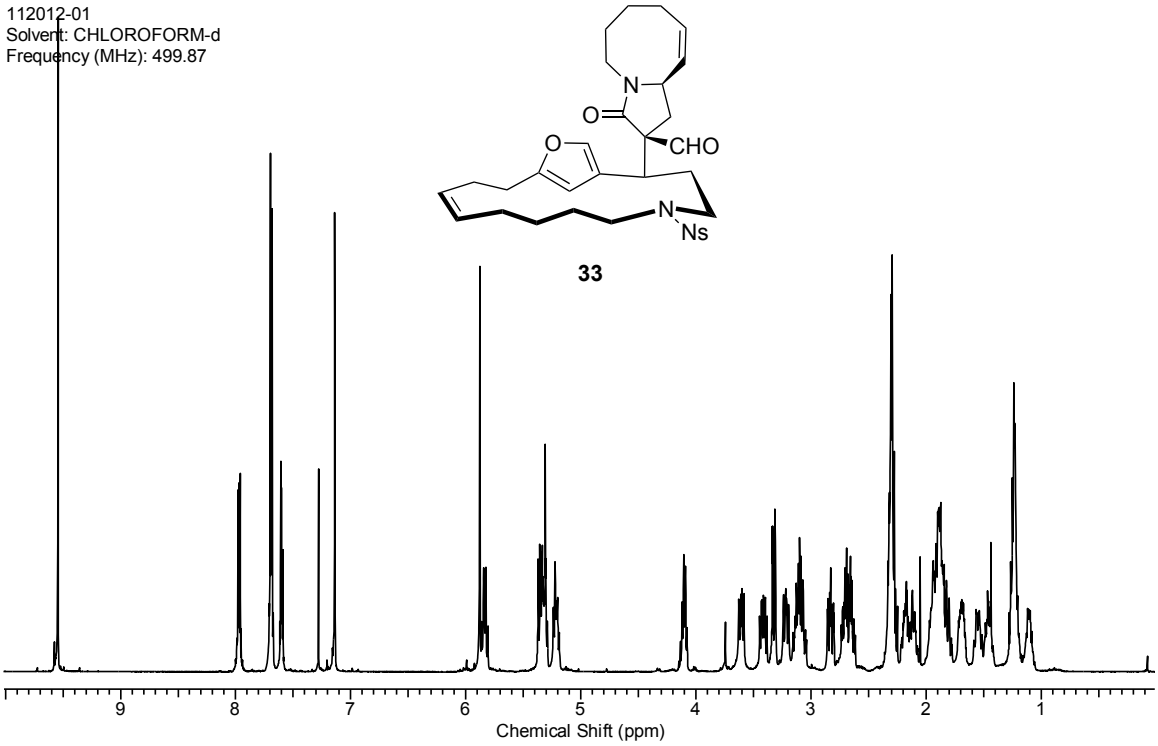
111512-10
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79

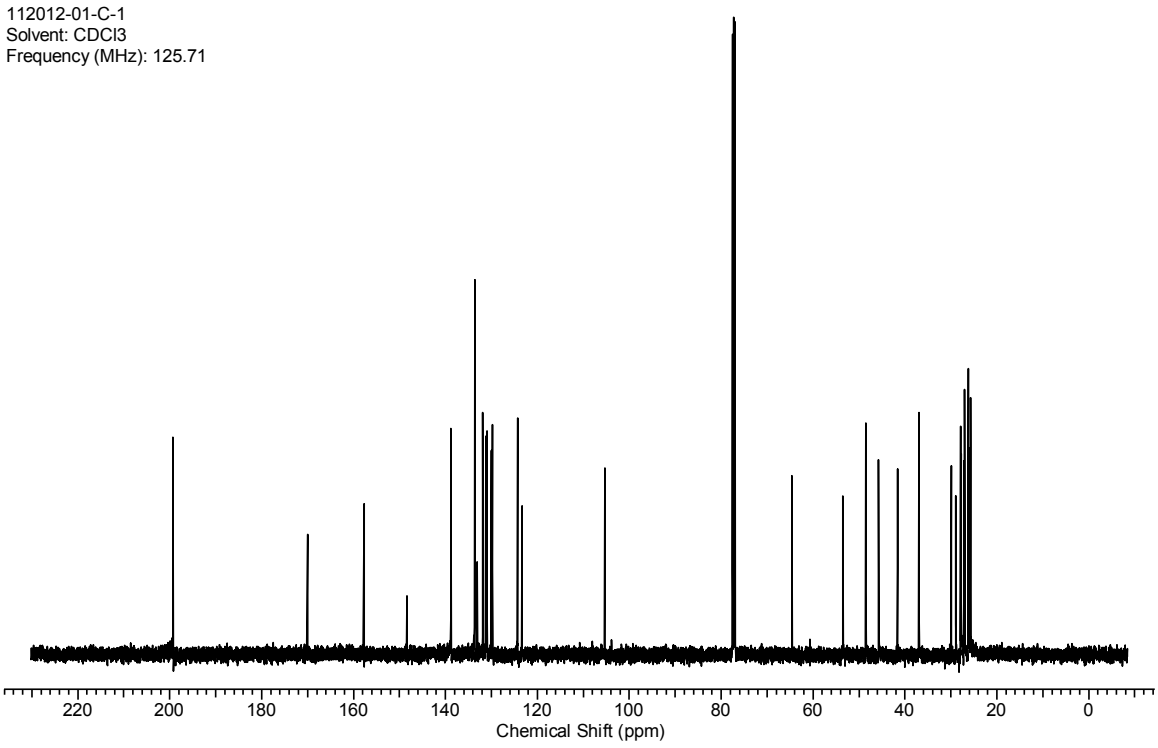


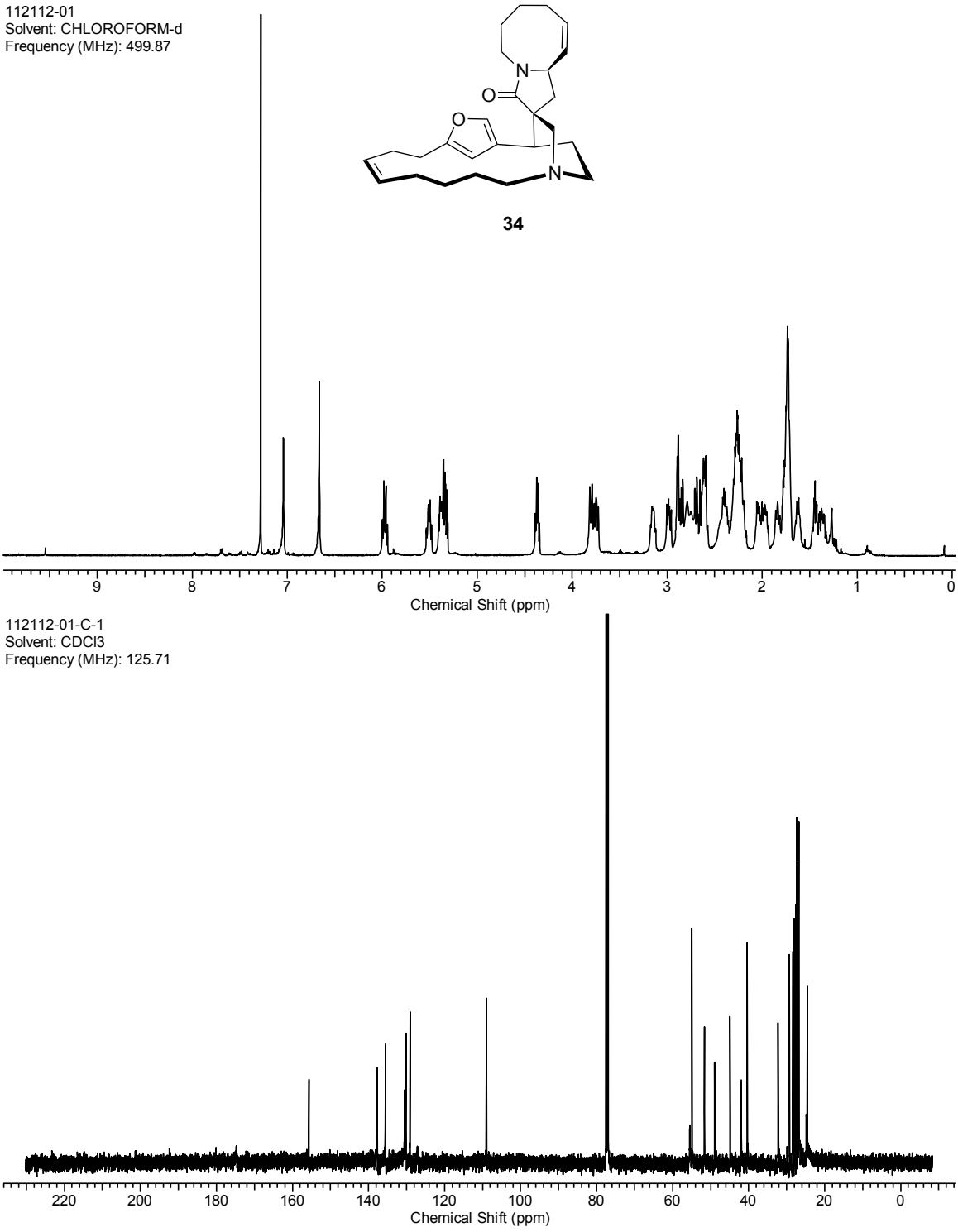


111312-03-C-1
Solvent: CDCl3
Frequency (MHz): 125.71




112012-01
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87
N
O
CHO
O
N
Ns
33
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

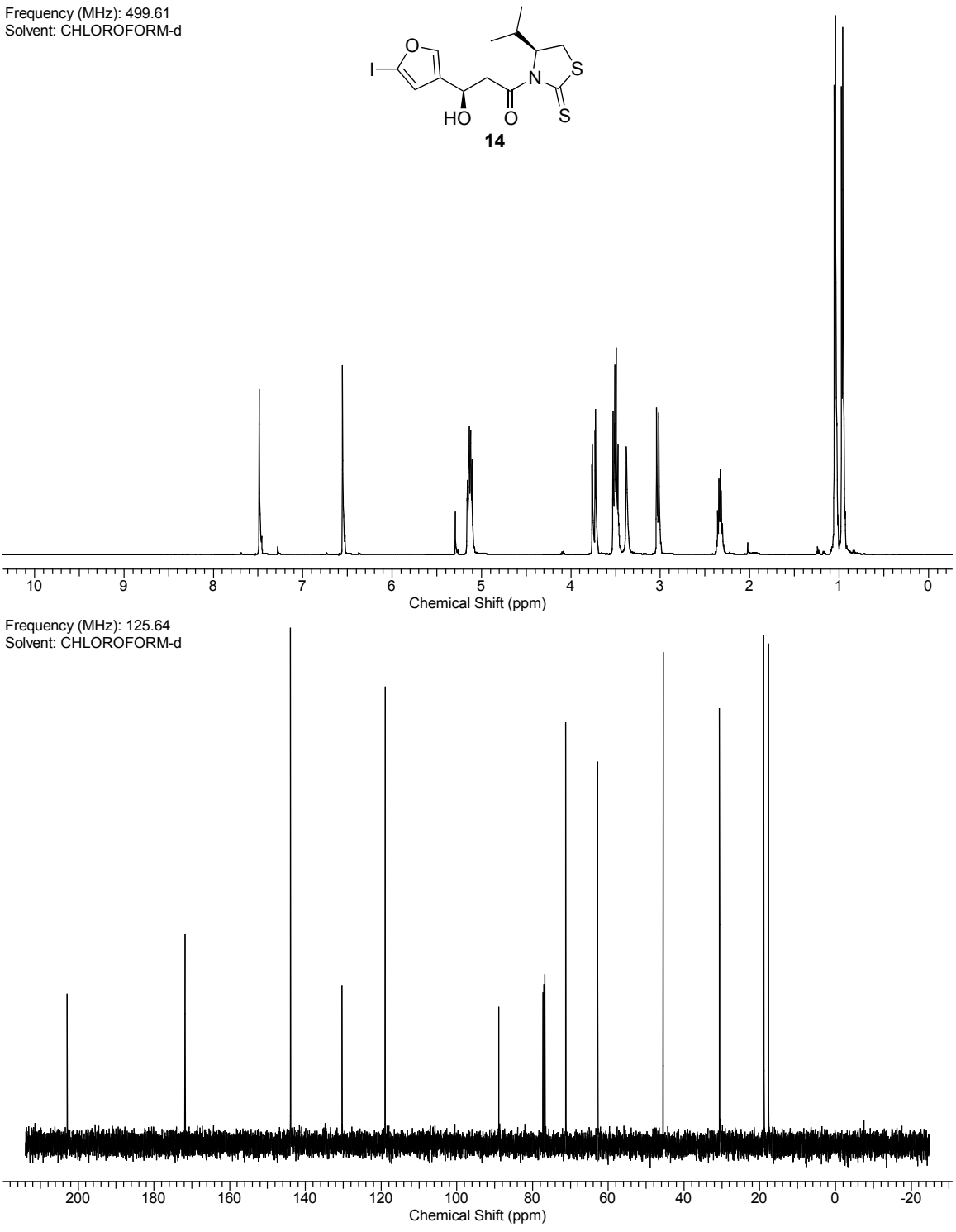

112012-01-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


112112-01
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87
N
O
O
N
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
112112-01-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

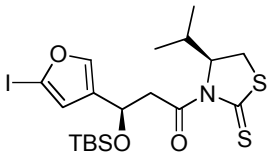
34

Appendix II

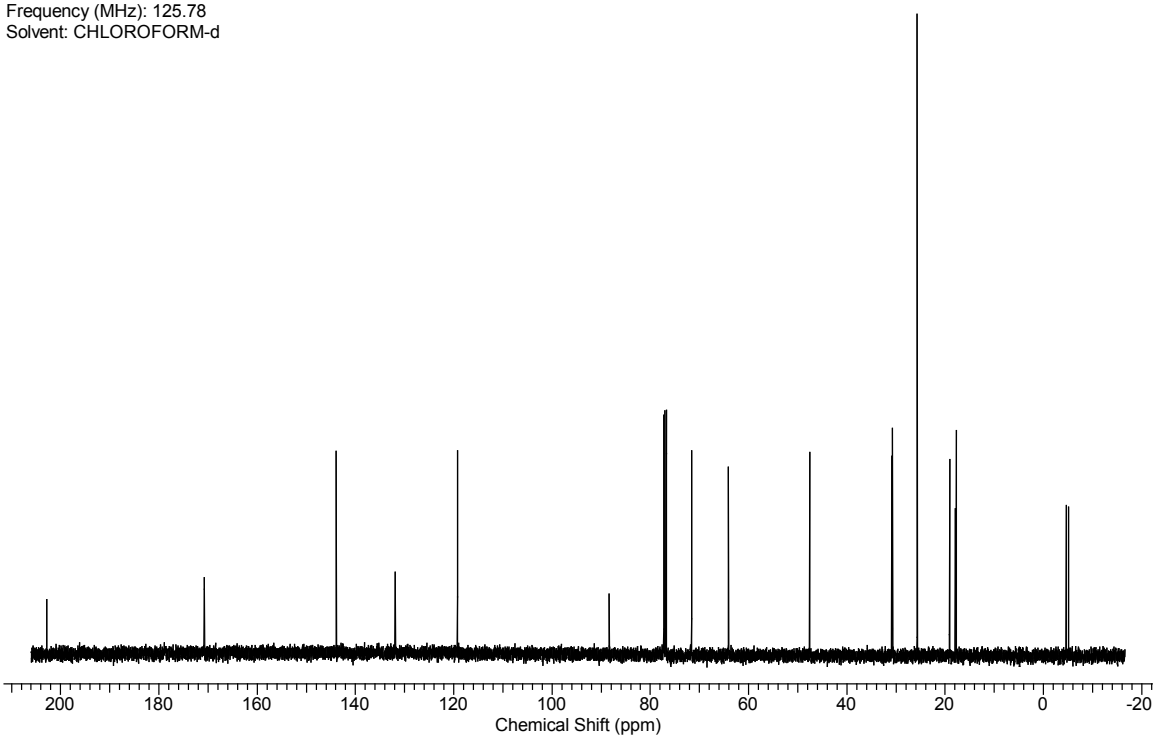
Chapter Three NMR Spectra

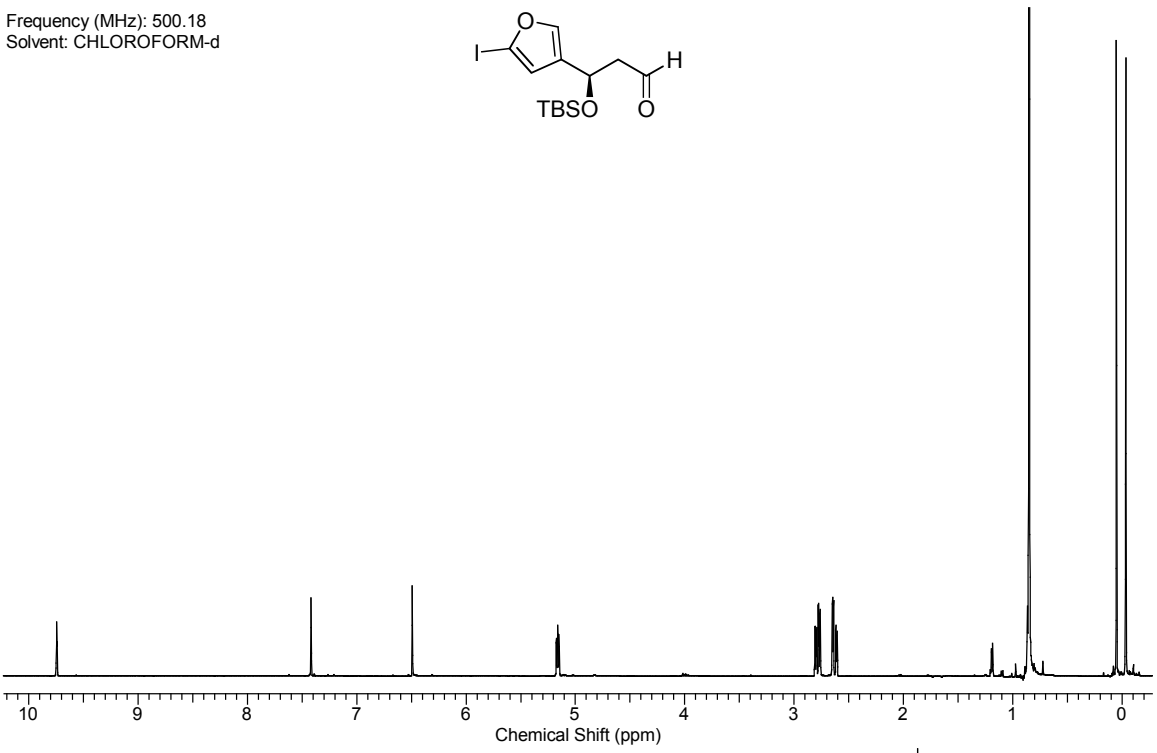

Frequency (MHz): 499.61
Solvent: CHLOROFORM-d
O
I
HO
O
N
S
S
14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
Frequency (MHz): 125.64
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

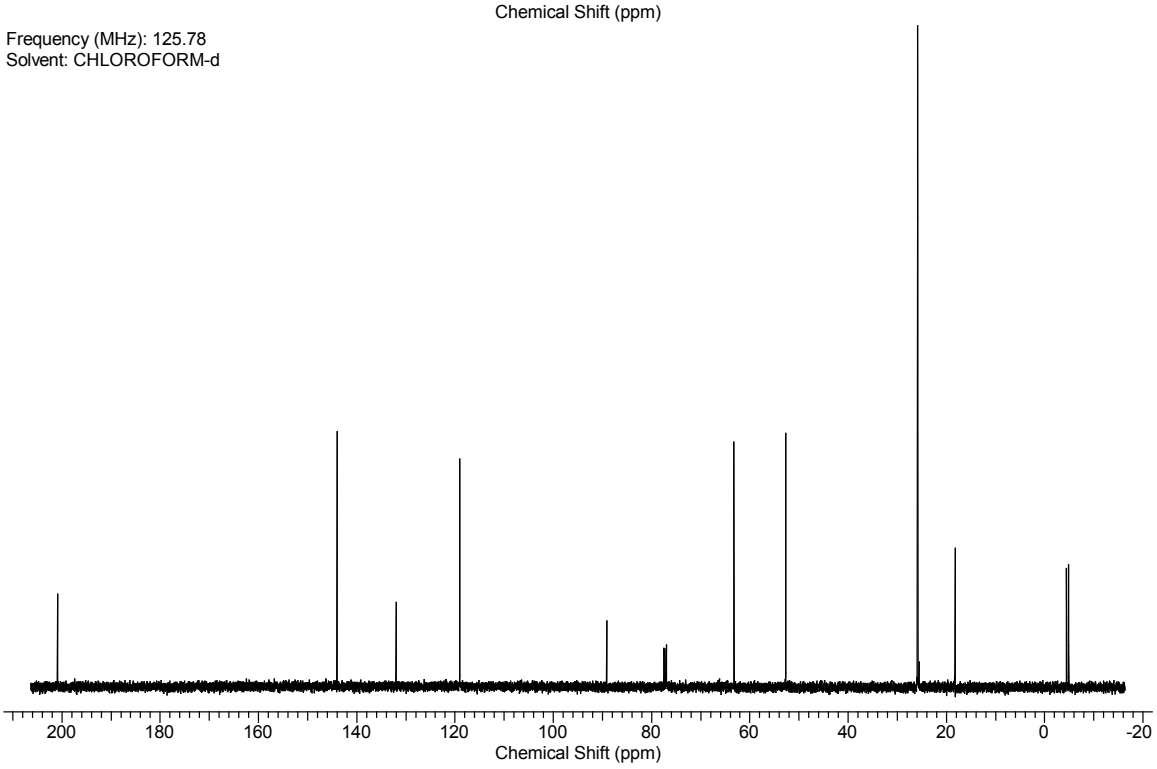
Frequency (MHz): 500.18
Solvent: CHLOROFORM-d

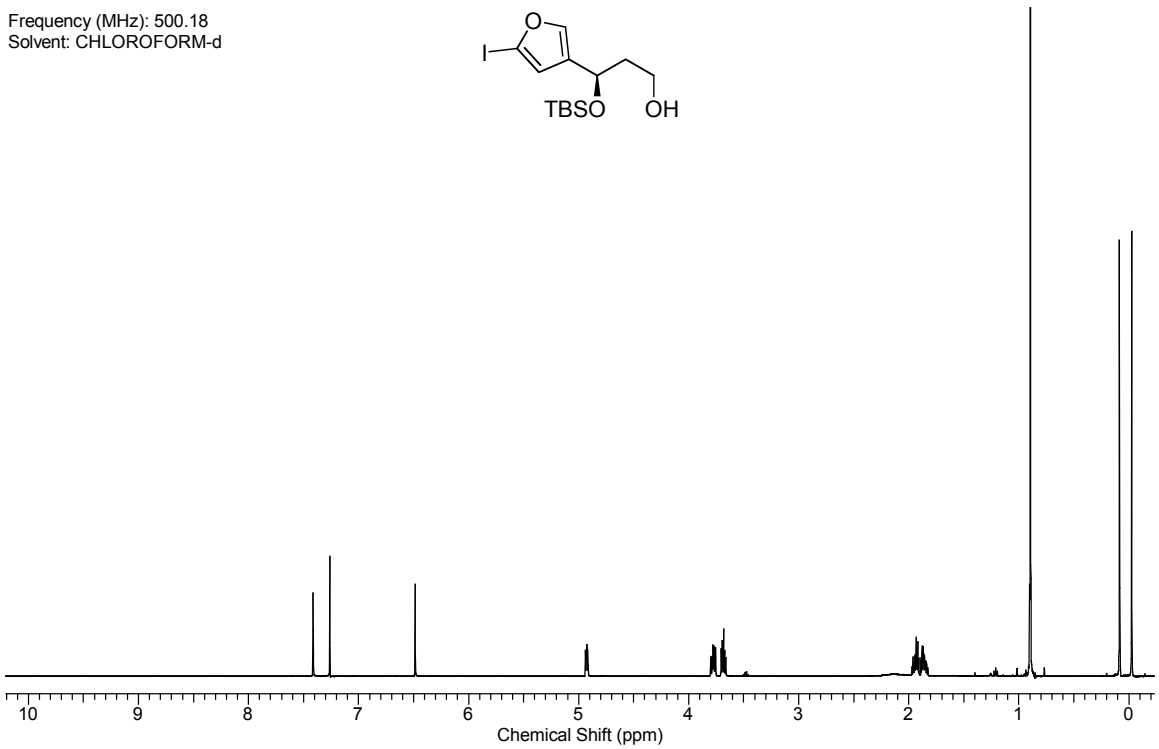


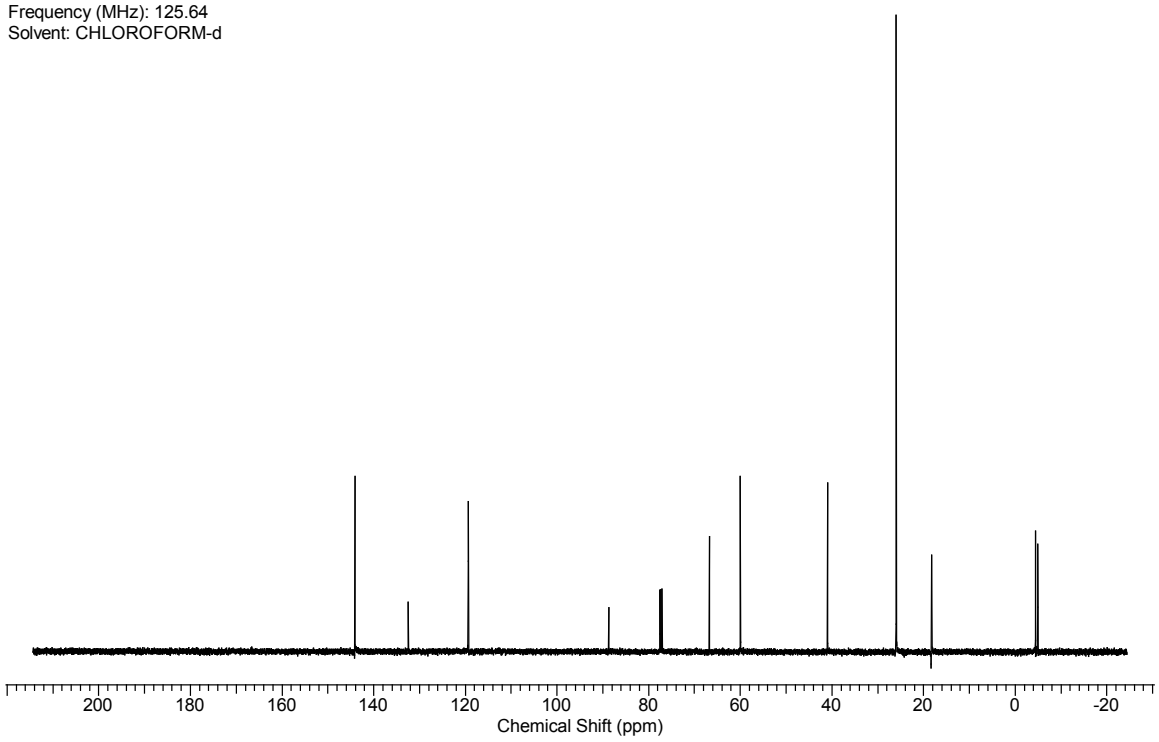
Frequency (MHz): 125.78
Solvent: CHLOROFORM-d



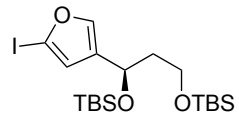

Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
O
I
H
TBSO
O
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
O
I
TBSO
OH
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

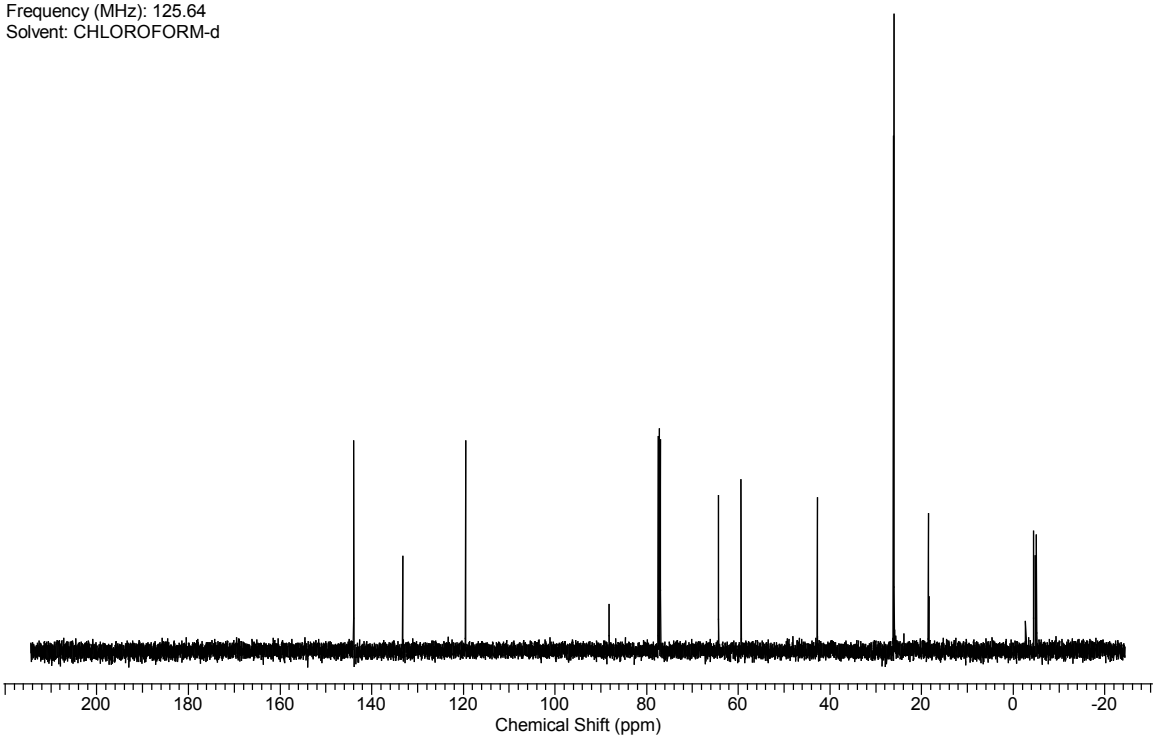

Frequency (MHz): 125.64
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

Frequency (MHz): 499.61
Solvent: CHLOROFORM-d

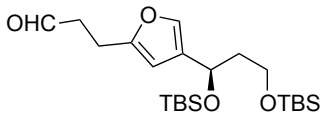


15

Frequency (MHz): 125.64
Solvent: CHLOROFORM-d

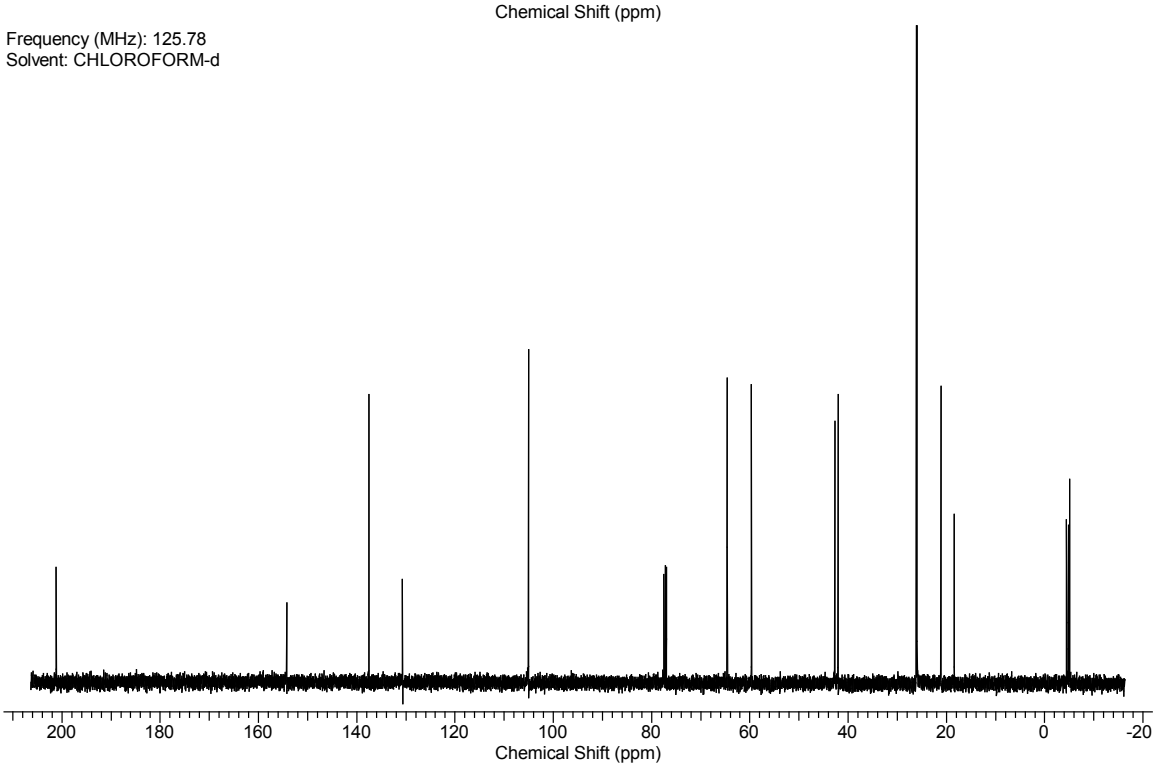


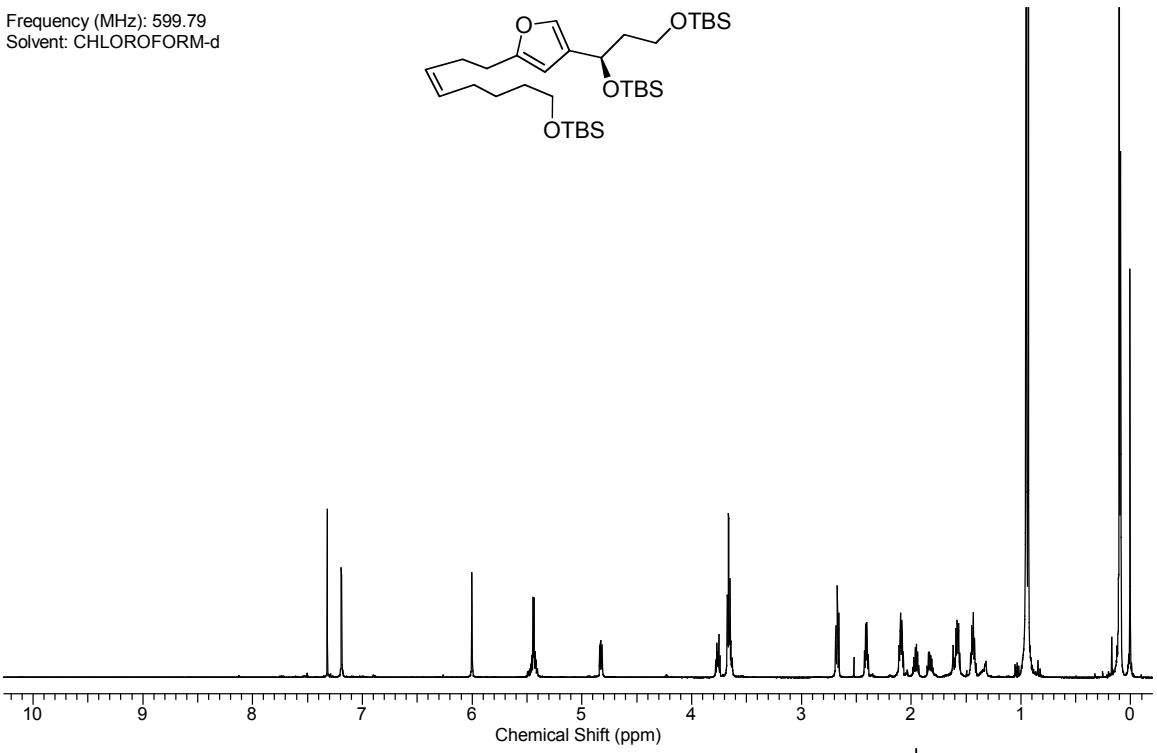
Frequency (MHz): 500.18
Solvent: CHLOROFORM-d

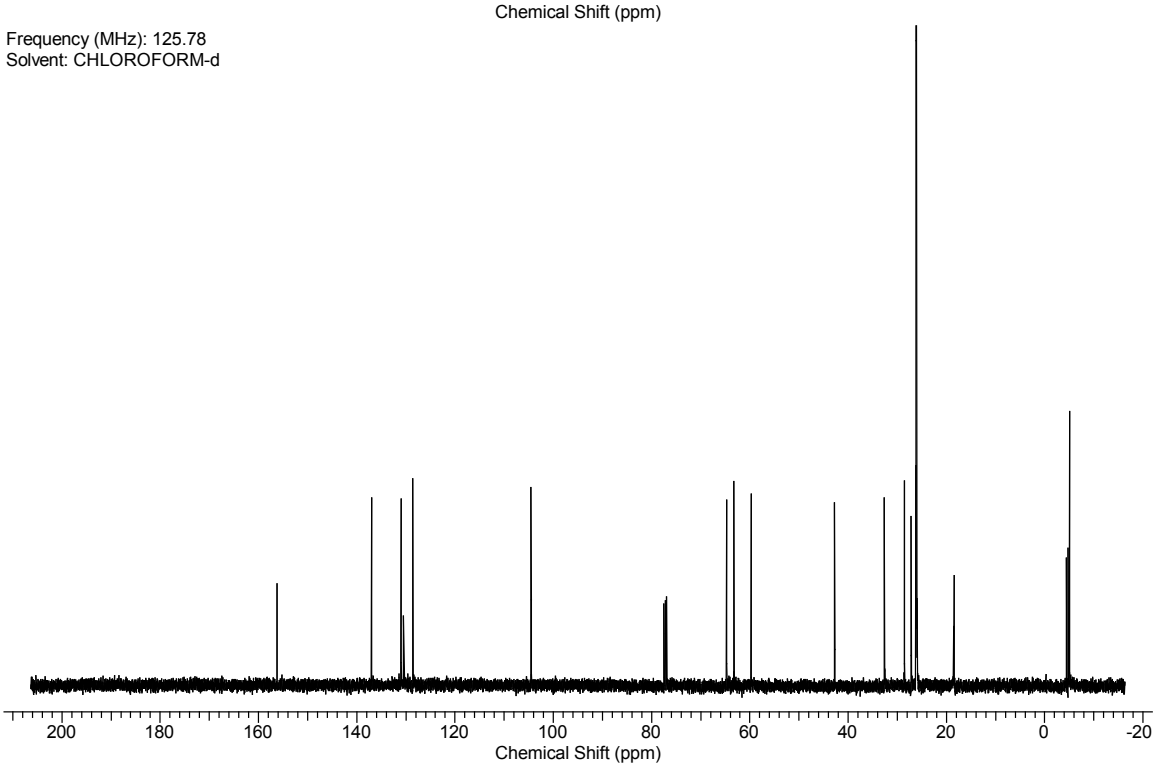


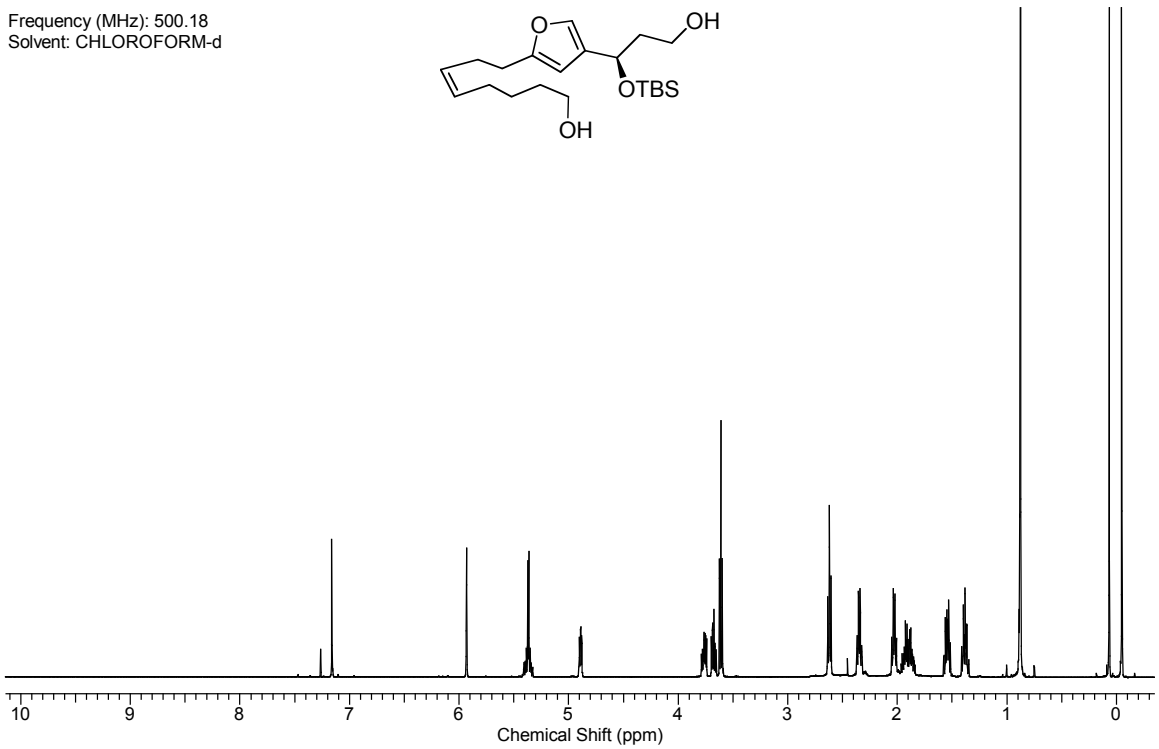
16

Frequency (MHz): 125.78
Solvent: CHLOROFORM-d

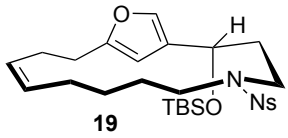



Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
O
OTBS
OTBS
OTBS
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

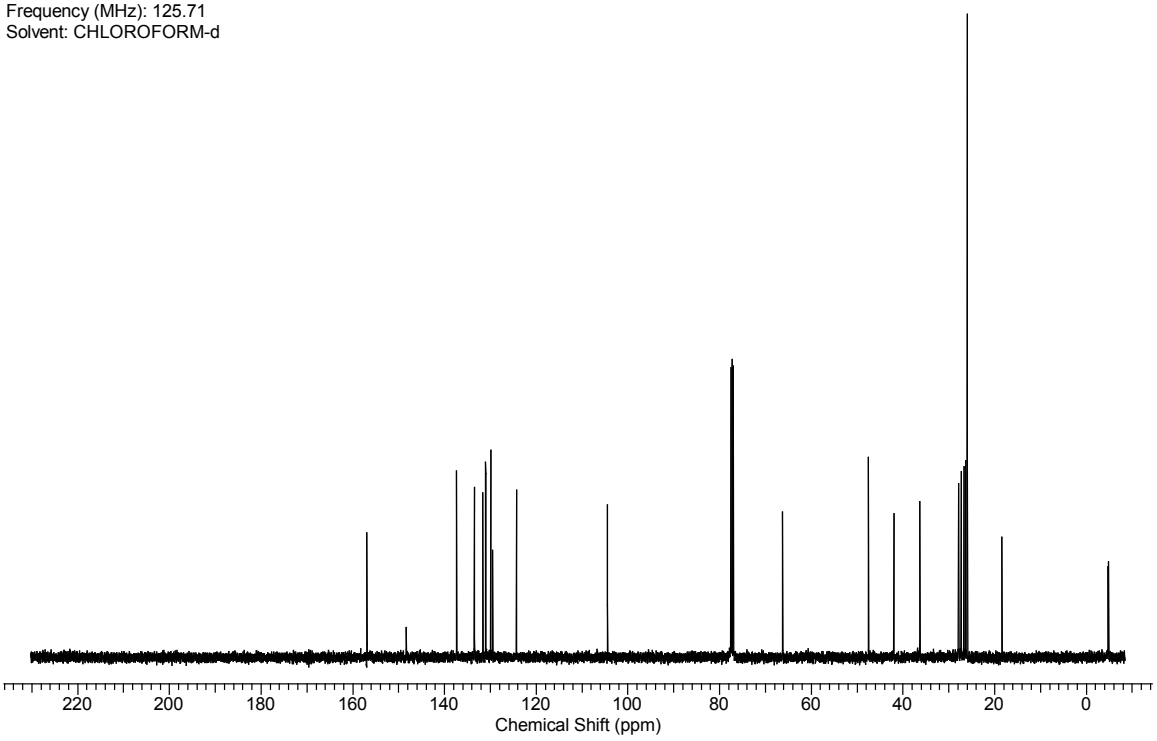

Frequency (MHz): 500.18
Solvent: CHLOROFORM-d
O
OH
OTBS
OH
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

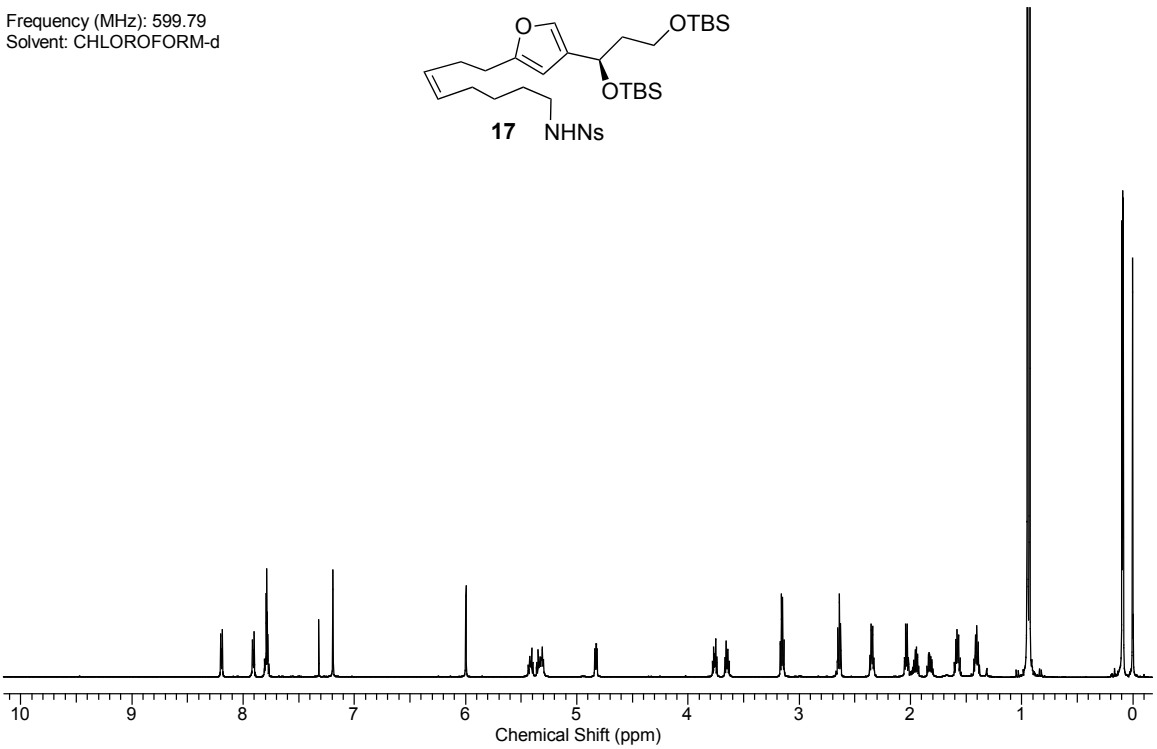
Frequency (MHz): 499.87
Solvent: CHLOROFORM-d

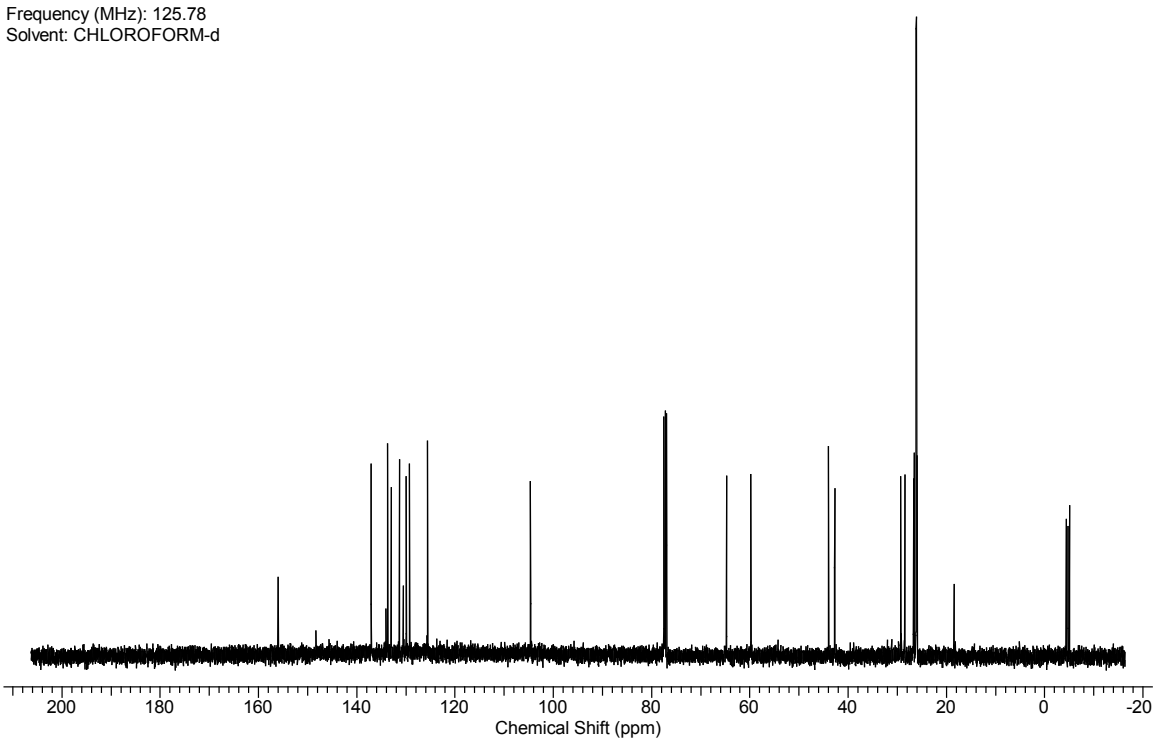


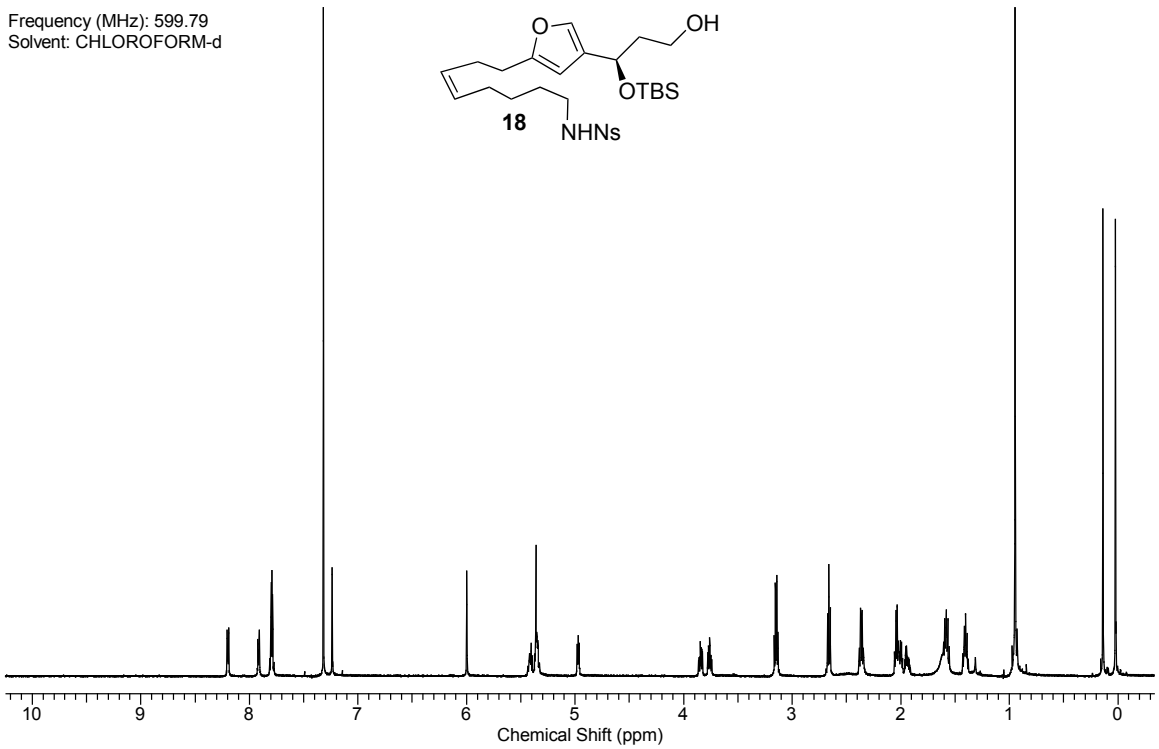
19

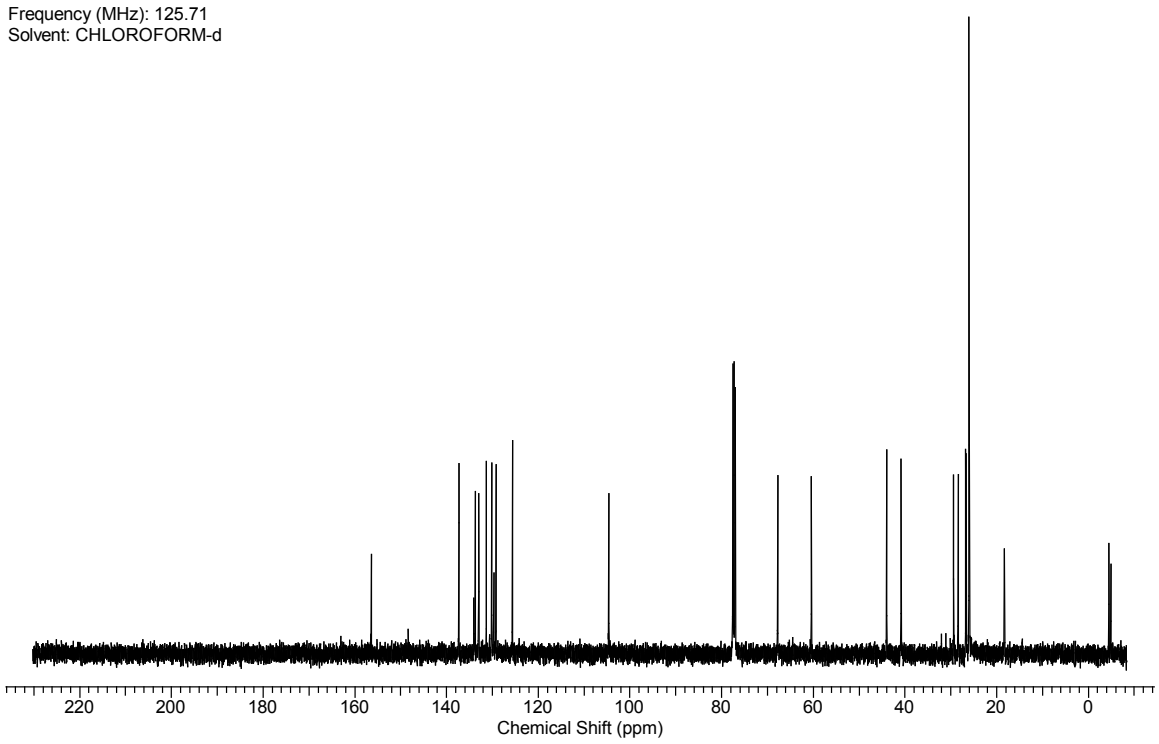
Frequency (MHz): 125.71
Solvent: CHLOROFORM-d

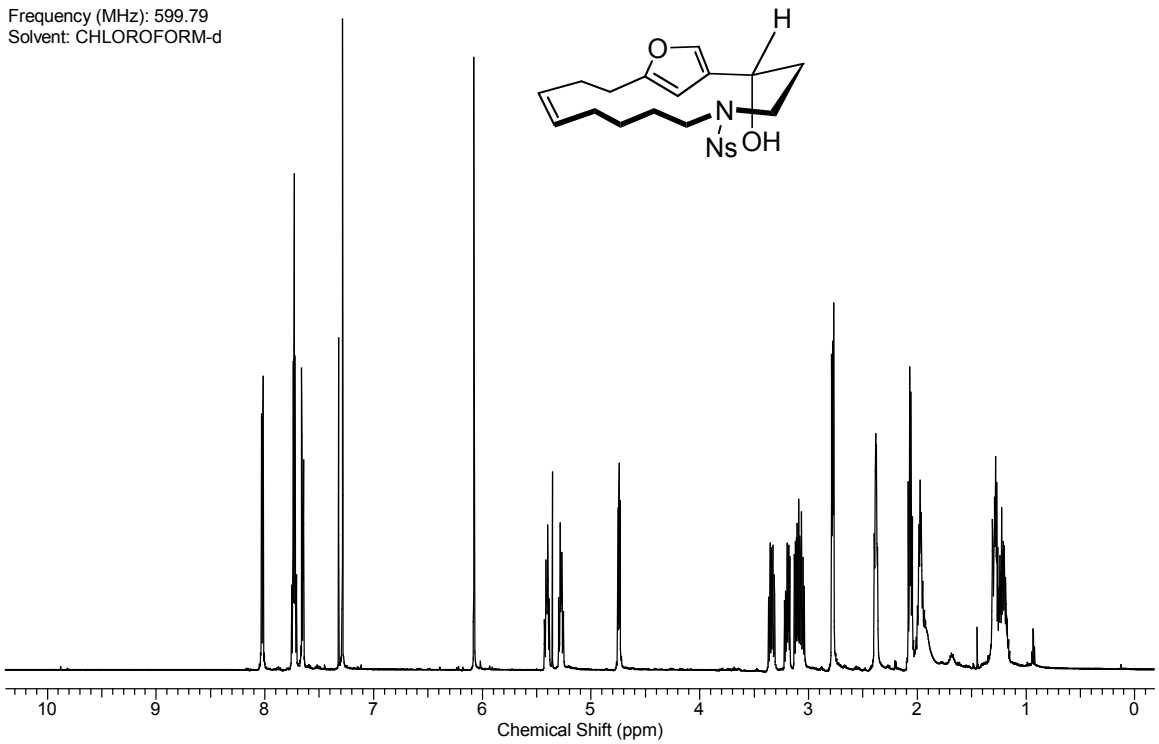


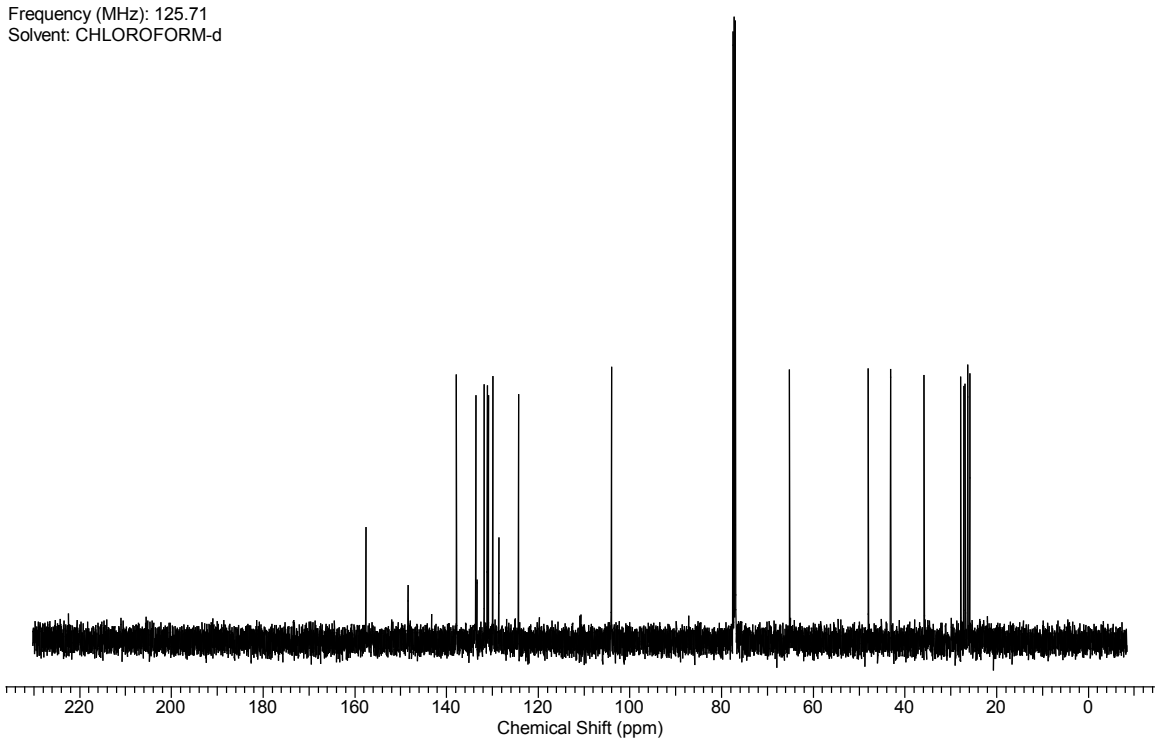

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
O
OTBS
OTBS
17 NHNs
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 125.78
Solvent: CHLOROFORM-d
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

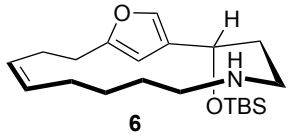

Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
O
OH
OTBS
18
NHNs
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Frequency (MHz): 125.71
Solvent: CHLOROFORM-d
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


Frequency (MHz): 599.79
Solvent: CHLOROFORM-d
H
O
N
Ns
OH
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

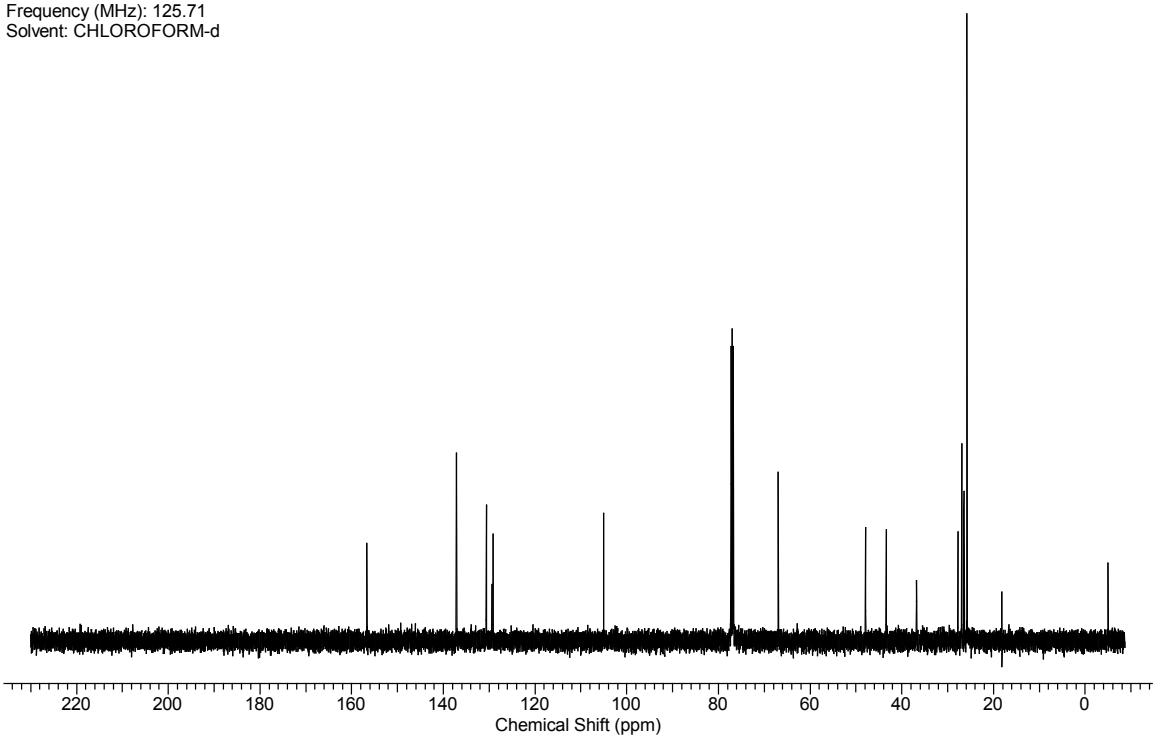

Frequency (MHz): 125.71
Solvent: CHLOROFORM-d
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

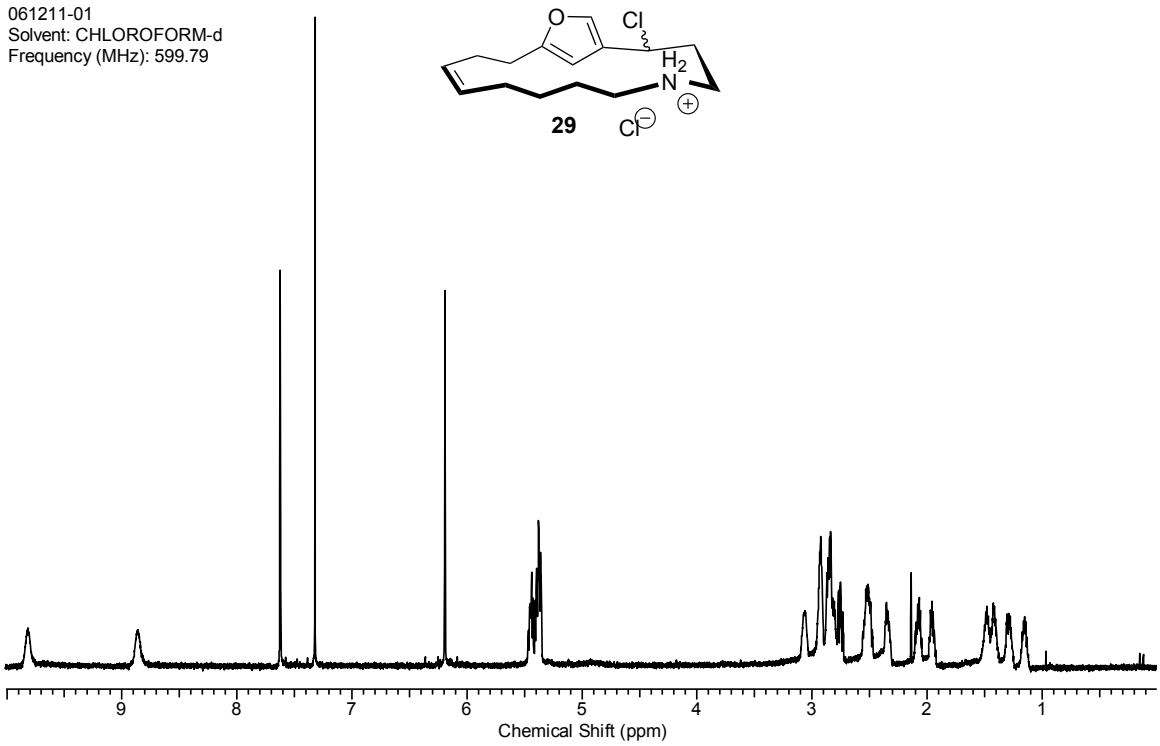
Frequency (MHz): 599.79
Solvent: CHLOROFORM-d

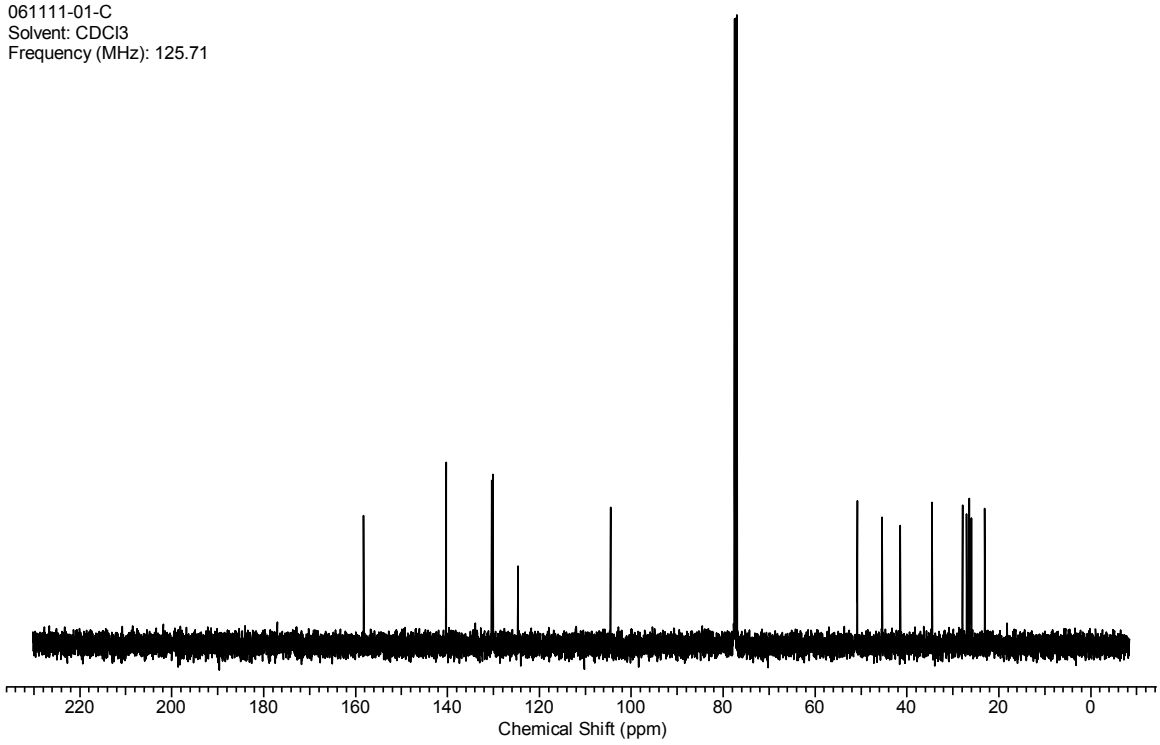


6

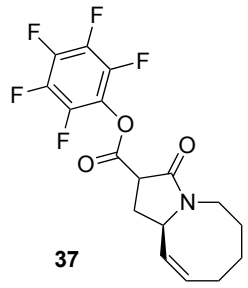
Frequency (MHz): 125.71
Solvent: CHLOROFORM-d



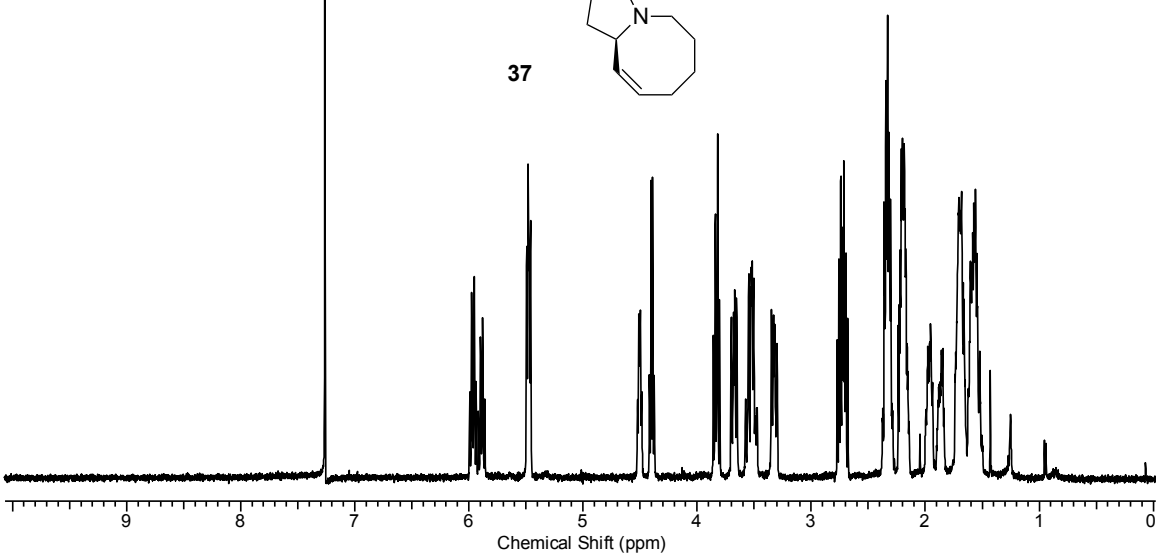

061211-01
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
O
Cl
H2
N
29
Cl
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


061111-01-C
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

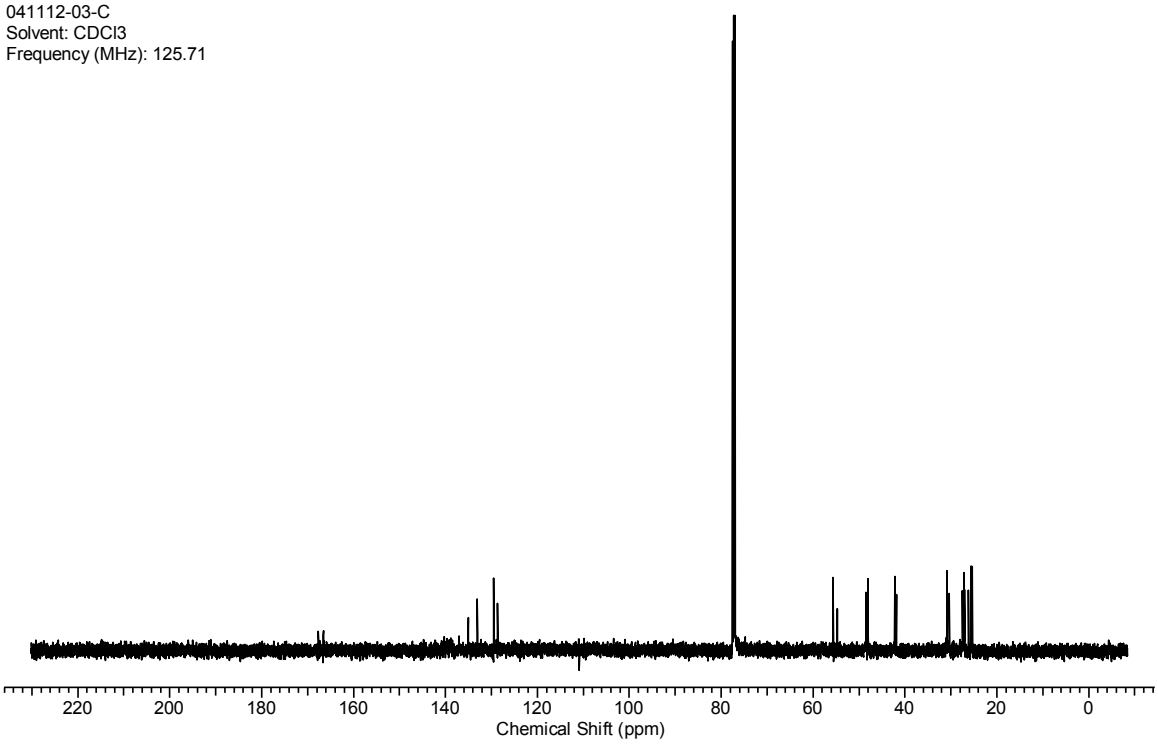
041112-03
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18

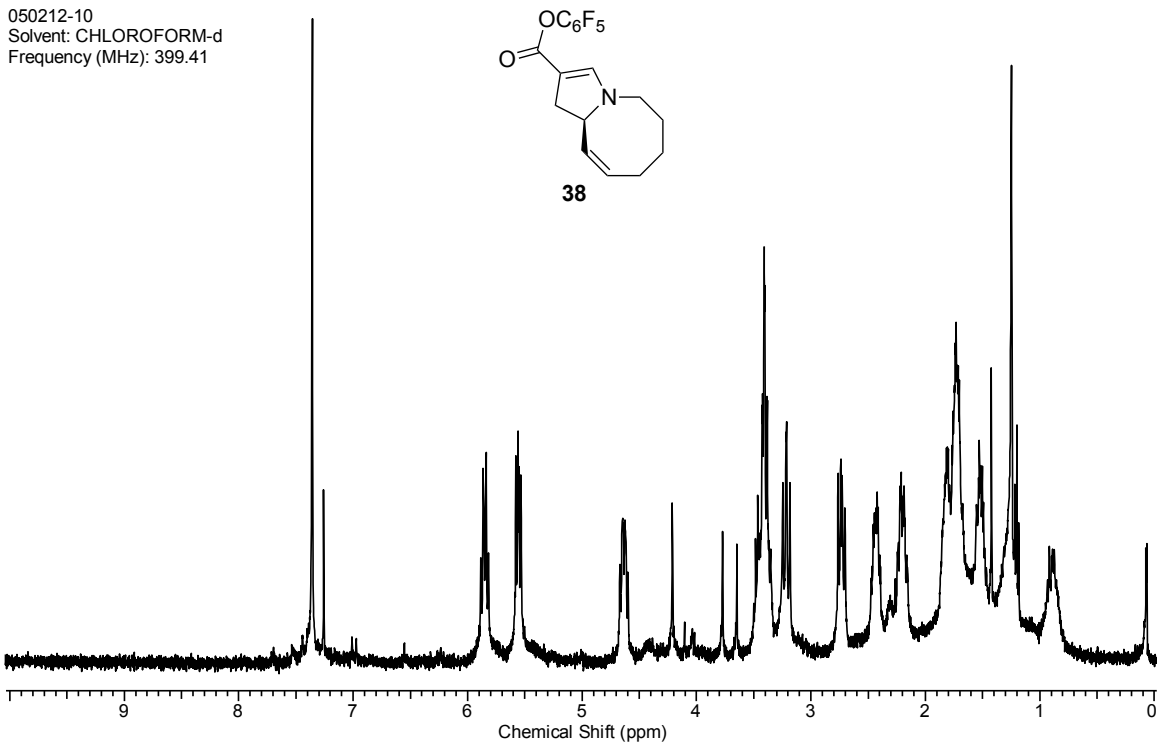


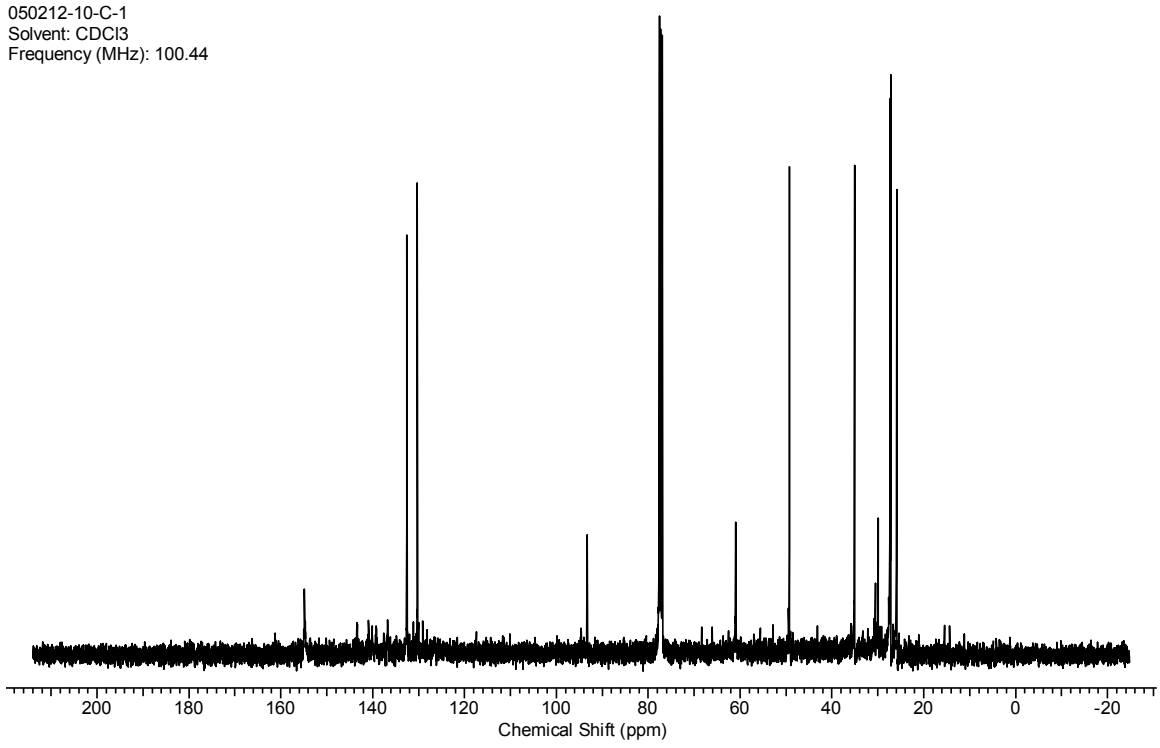
37

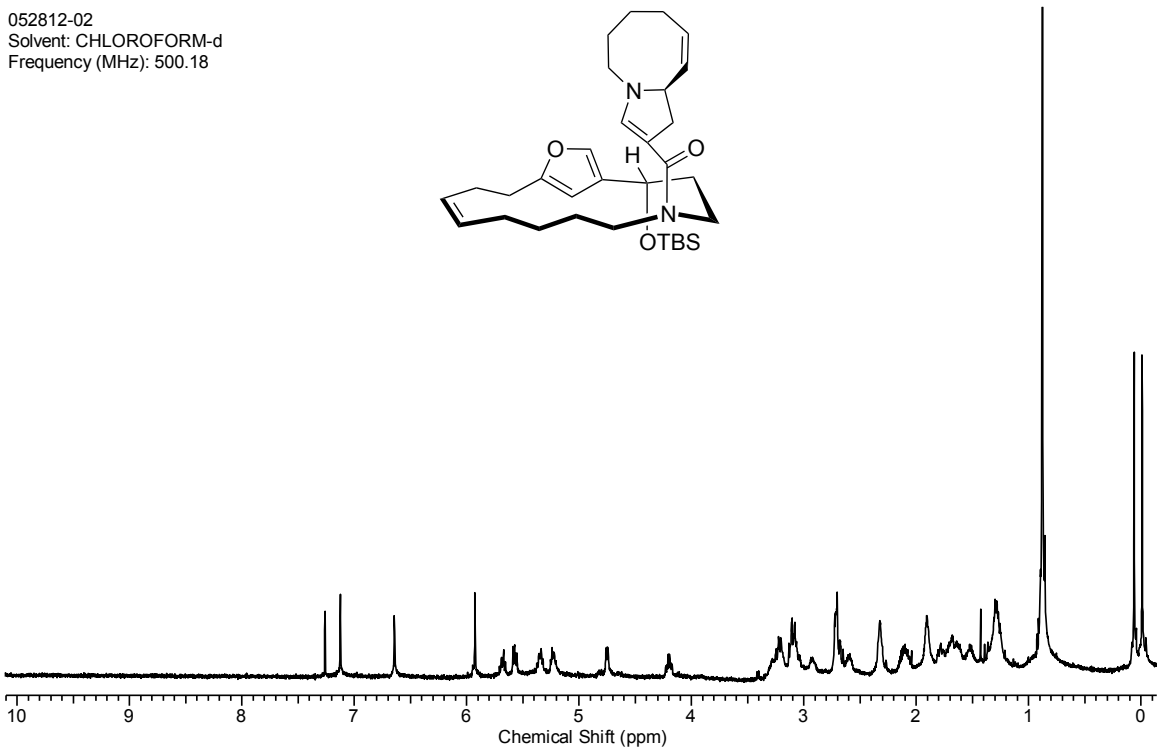


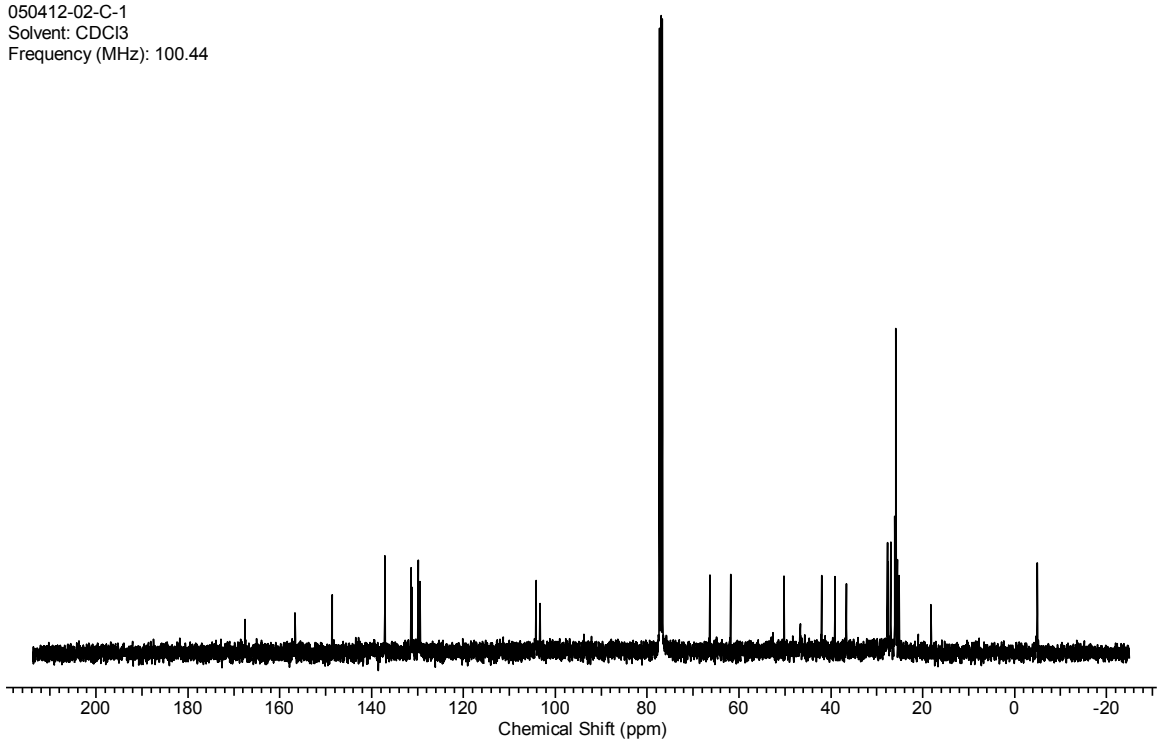
041112-03-C
Solvent: CDCl3
Frequency (MHz): 125.71

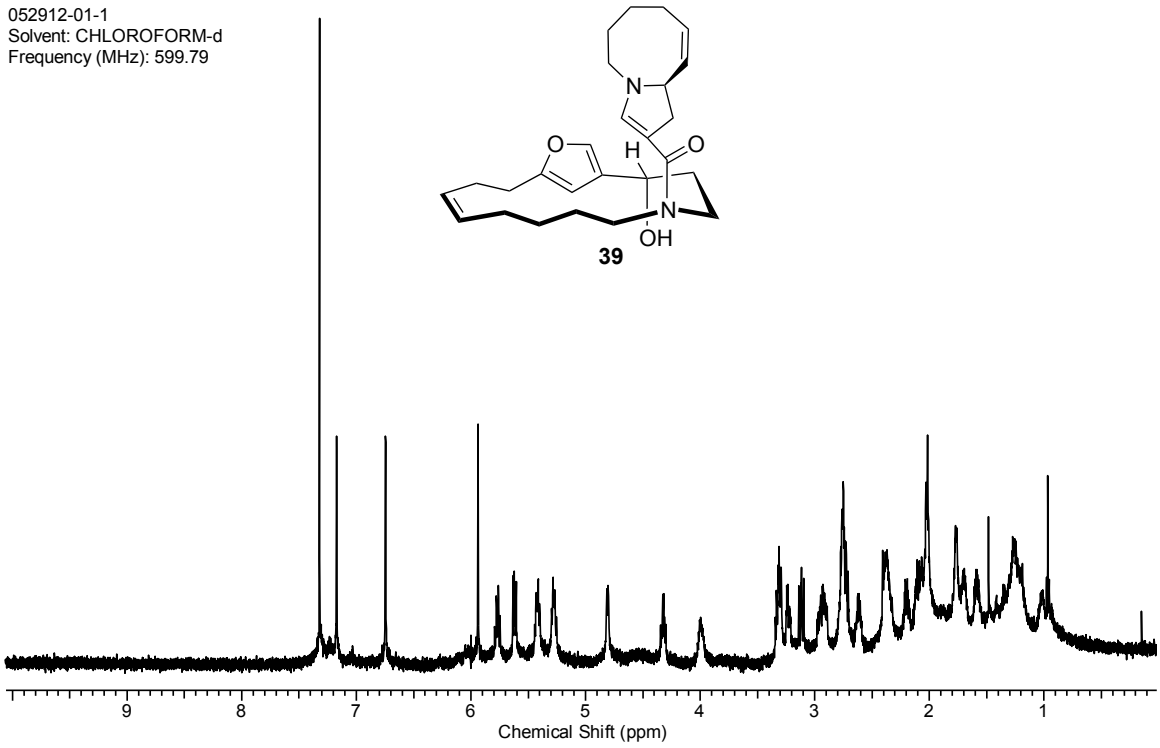



050212-10
Solvent: CHLOROFORM-d
Frequency (MHz): 399.41
OC6F5
O
N
38
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

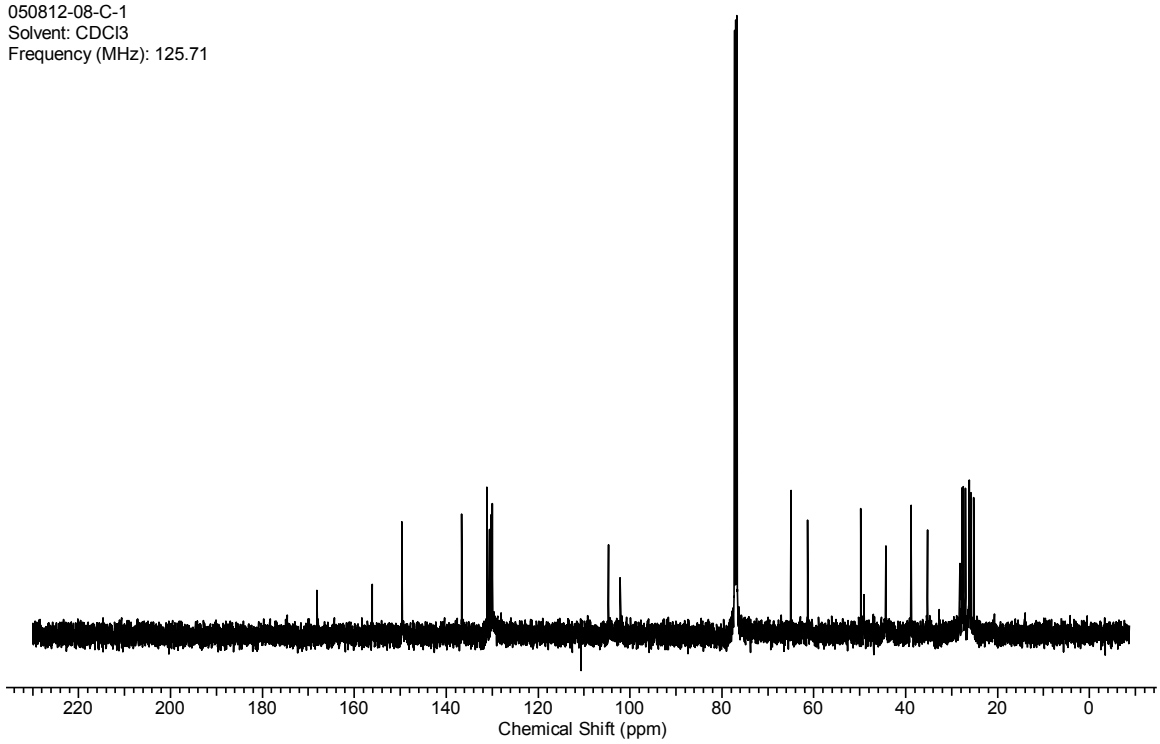

050212-10-C-1
Solvent: CDCl3
Frequency (MHz): 100.44
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

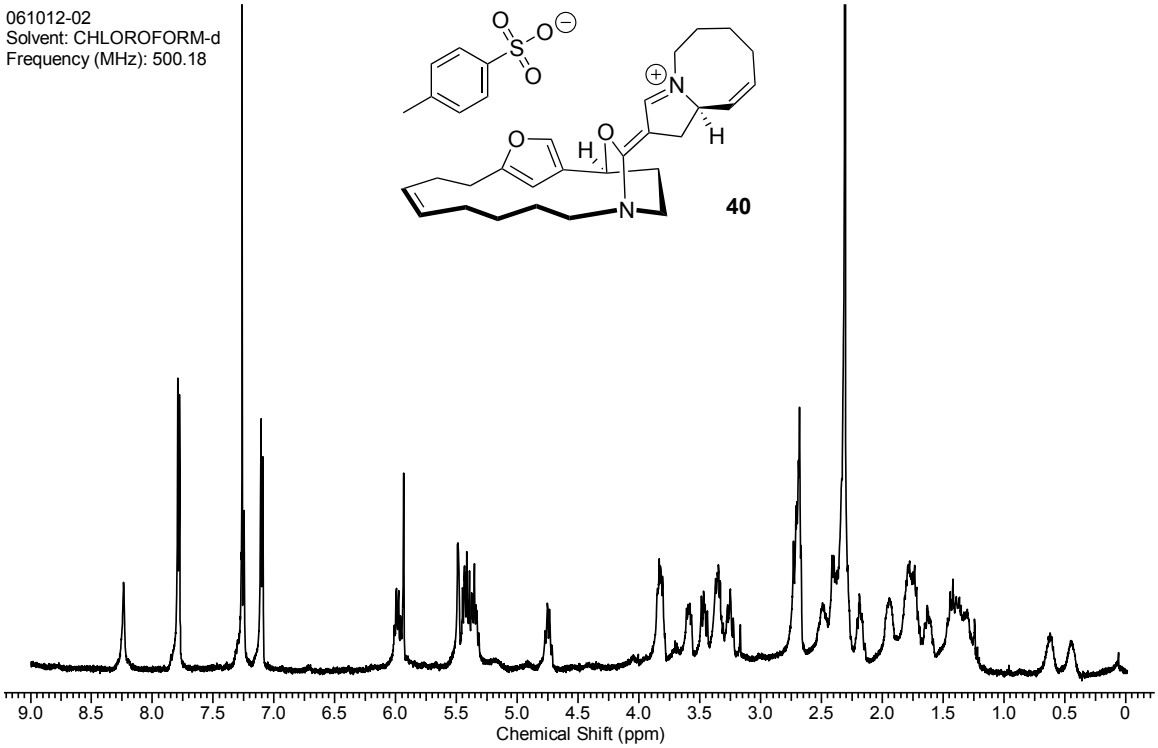

052812-02
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18
N
O
H
O
N
OTBS
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

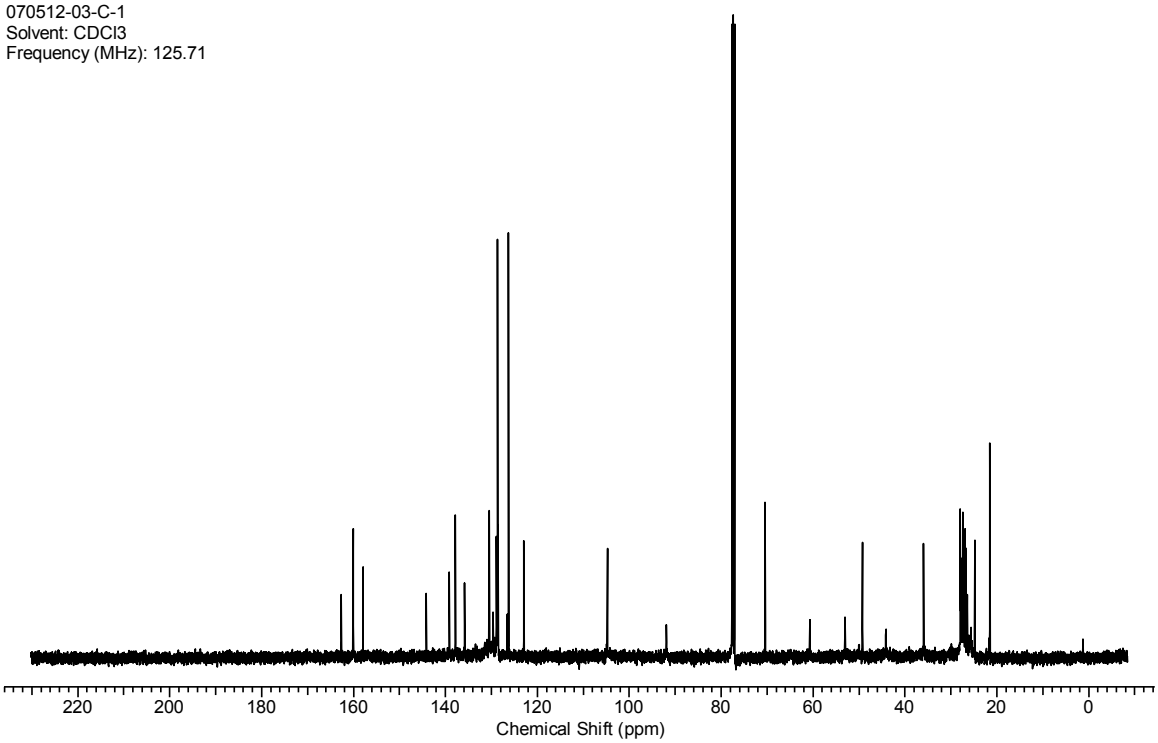

050412-02-C-1
Solvent: CDCl3
Frequency (MHz): 100.44
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


052912-01-1
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
N
O
H
O
N
OH
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

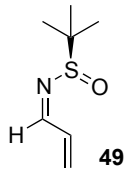
39


050812-08-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


061012-02
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18
40
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

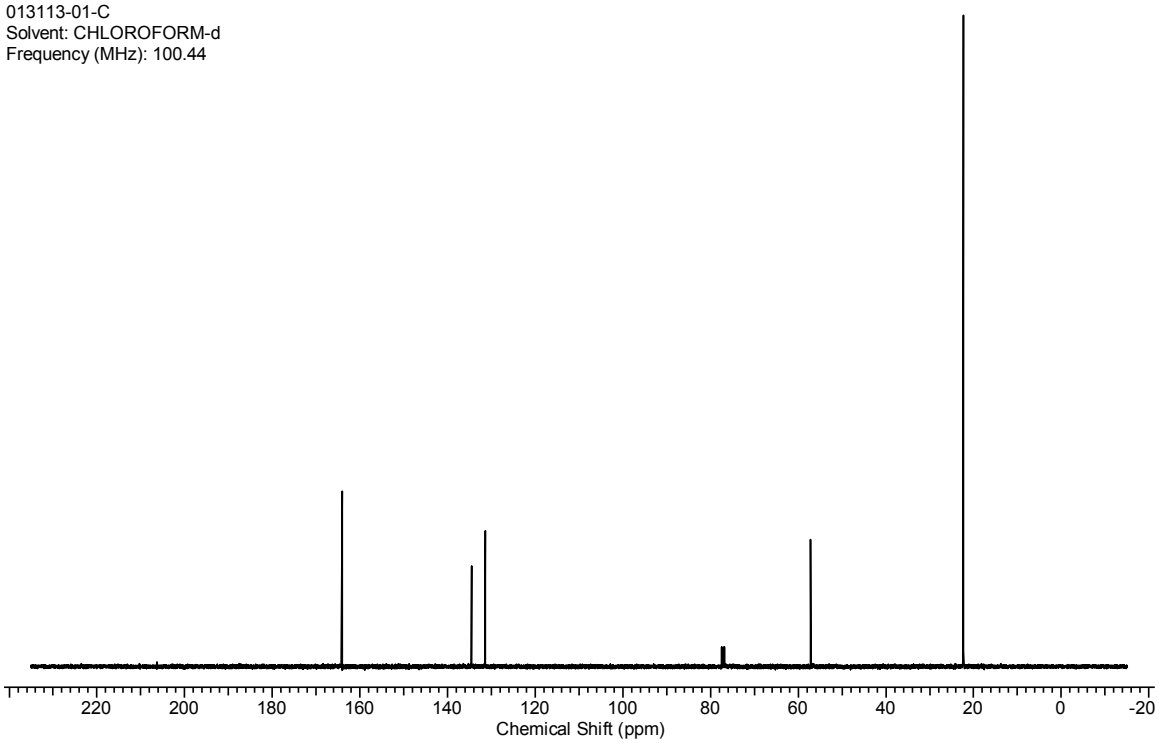

070512-03-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220 200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)

013113-01
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18

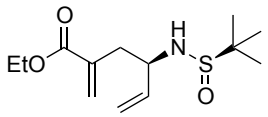


49

013113-01-C
Solvent: CHLOROFORM-d
Frequency (MHz): 100.44

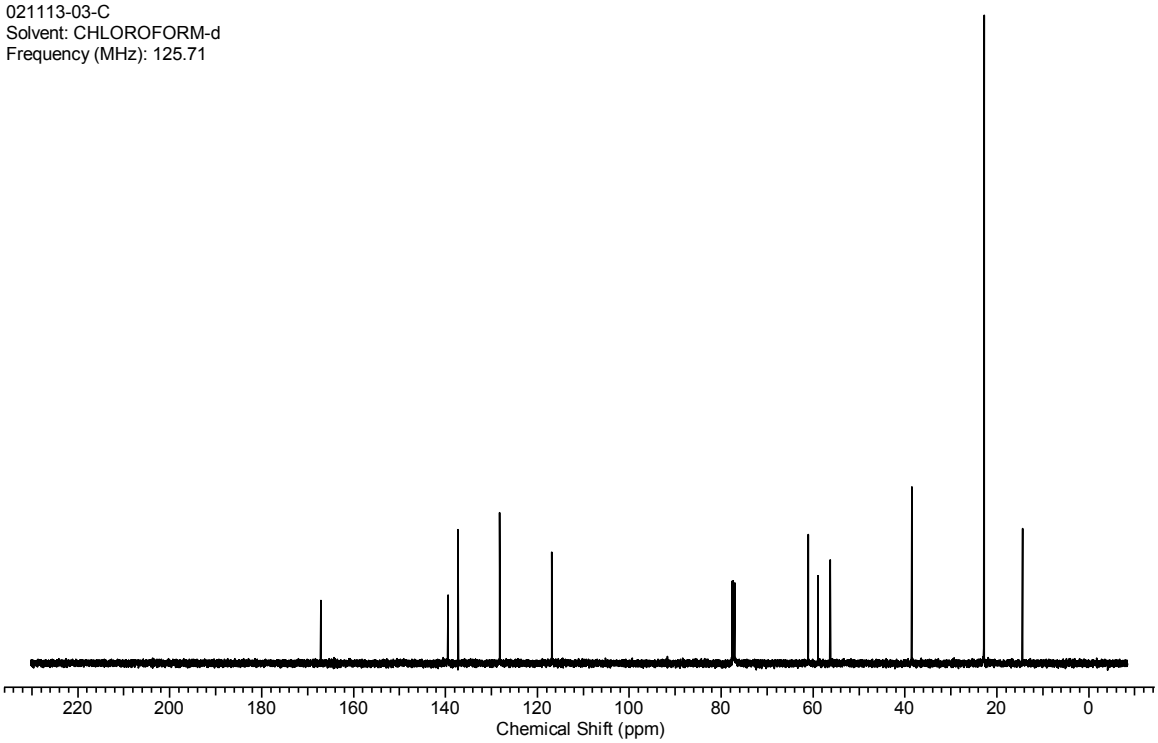


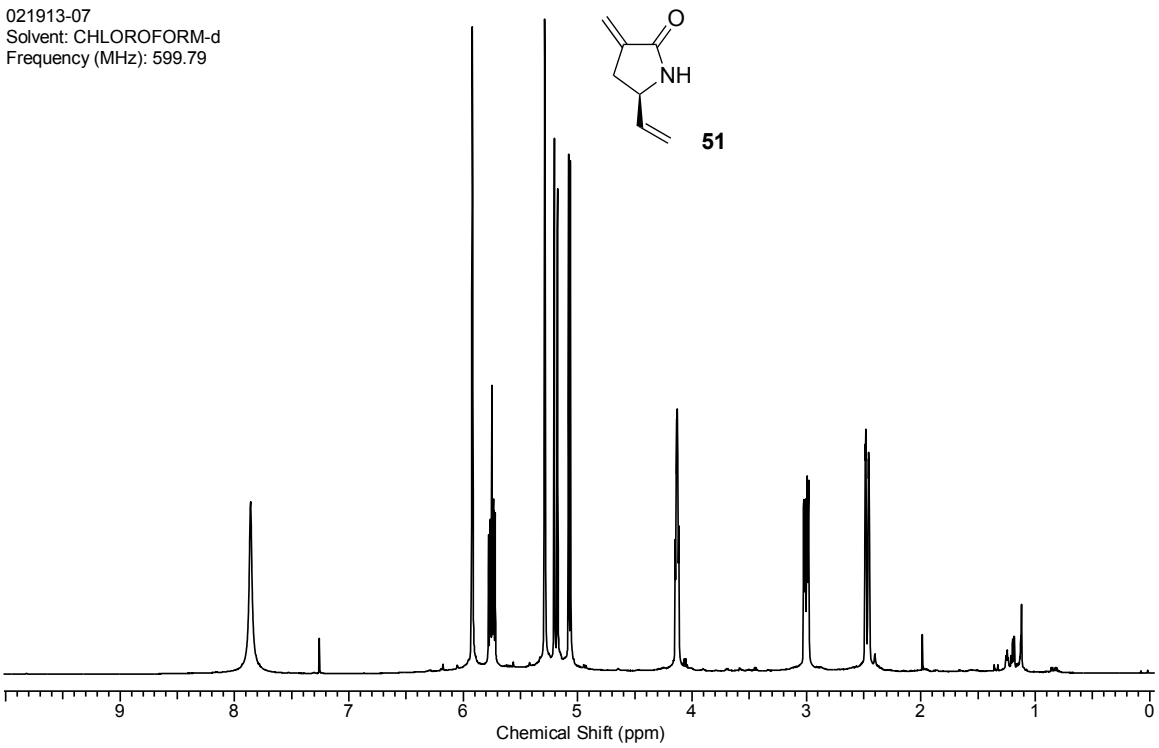
021113-03
Solvent: CDCl3
Frequency (MHz): 500.18

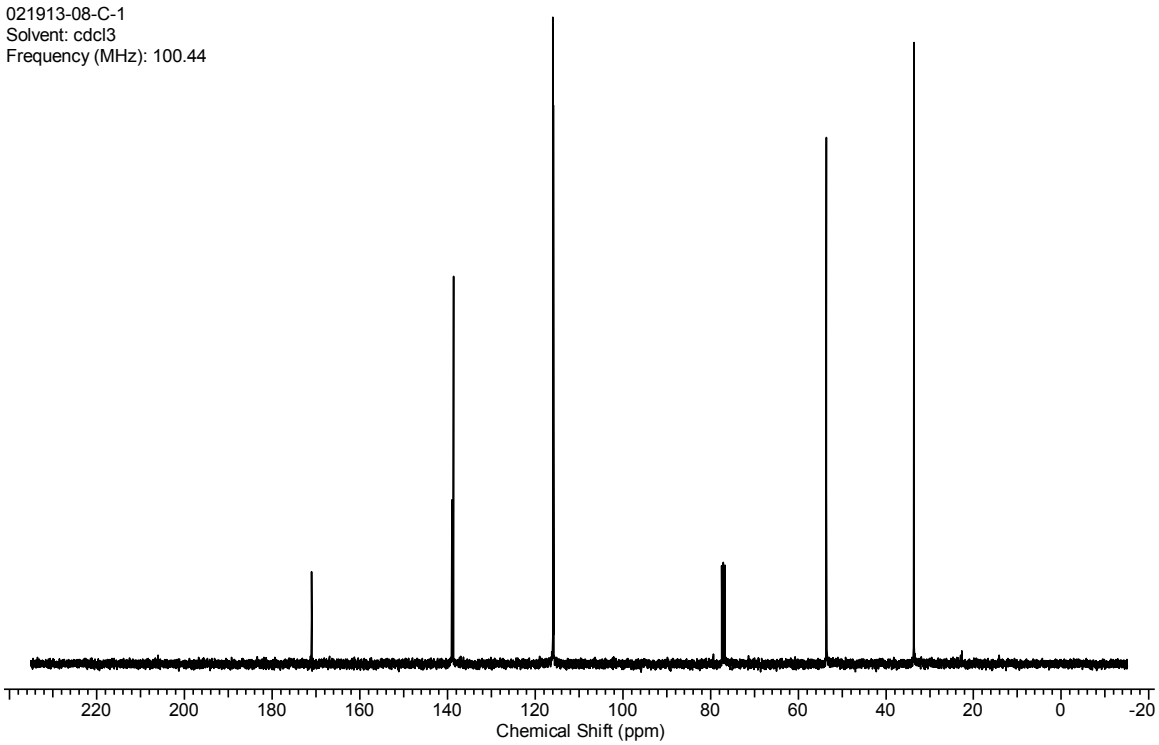


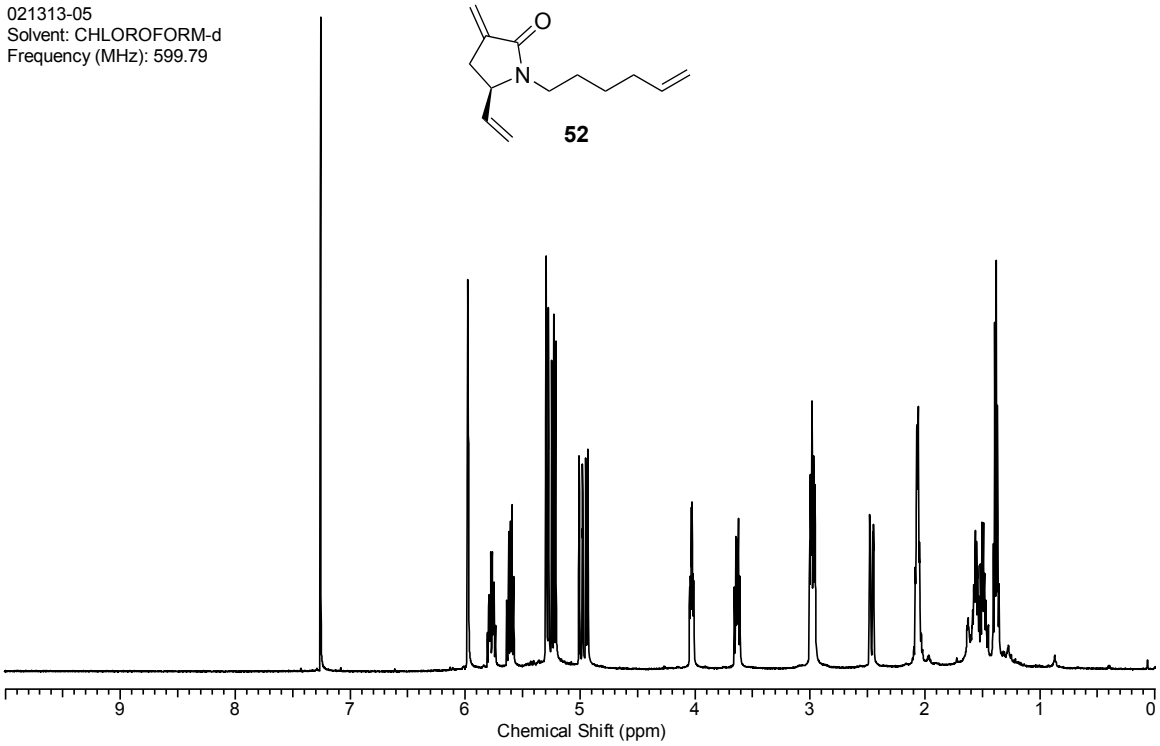
50

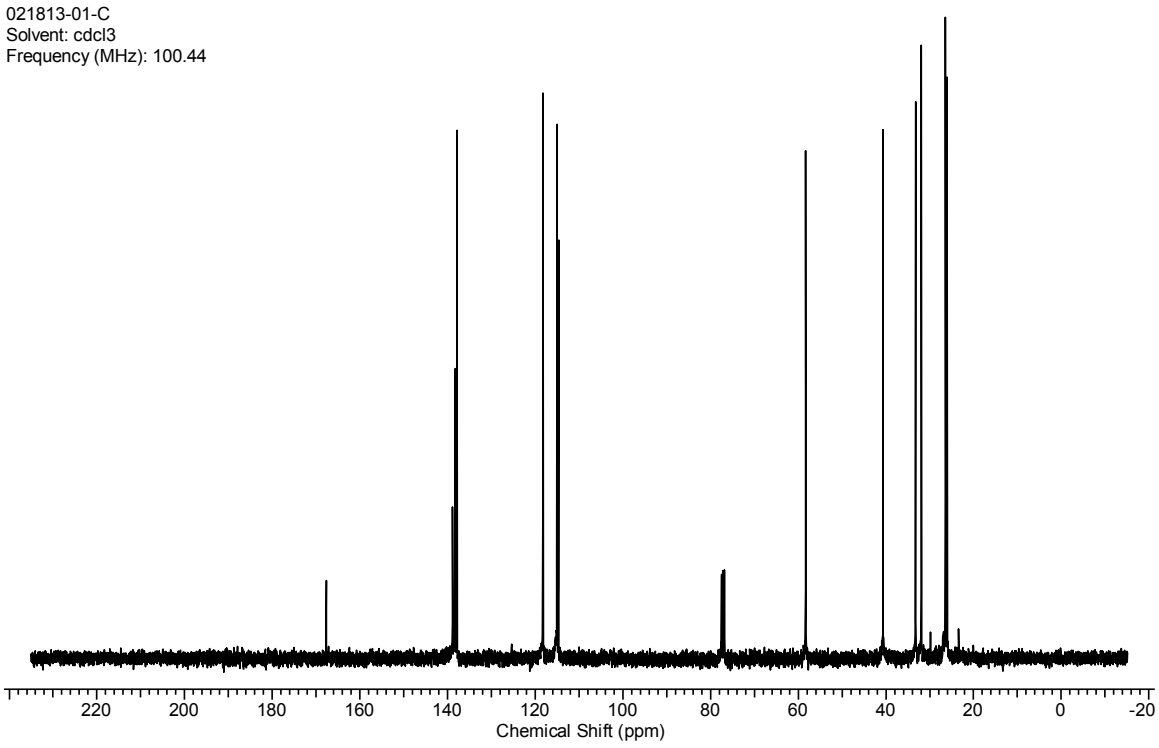
021113-03-C
Solvent: CHLOROFORM-d
Frequency (MHz): 125.71

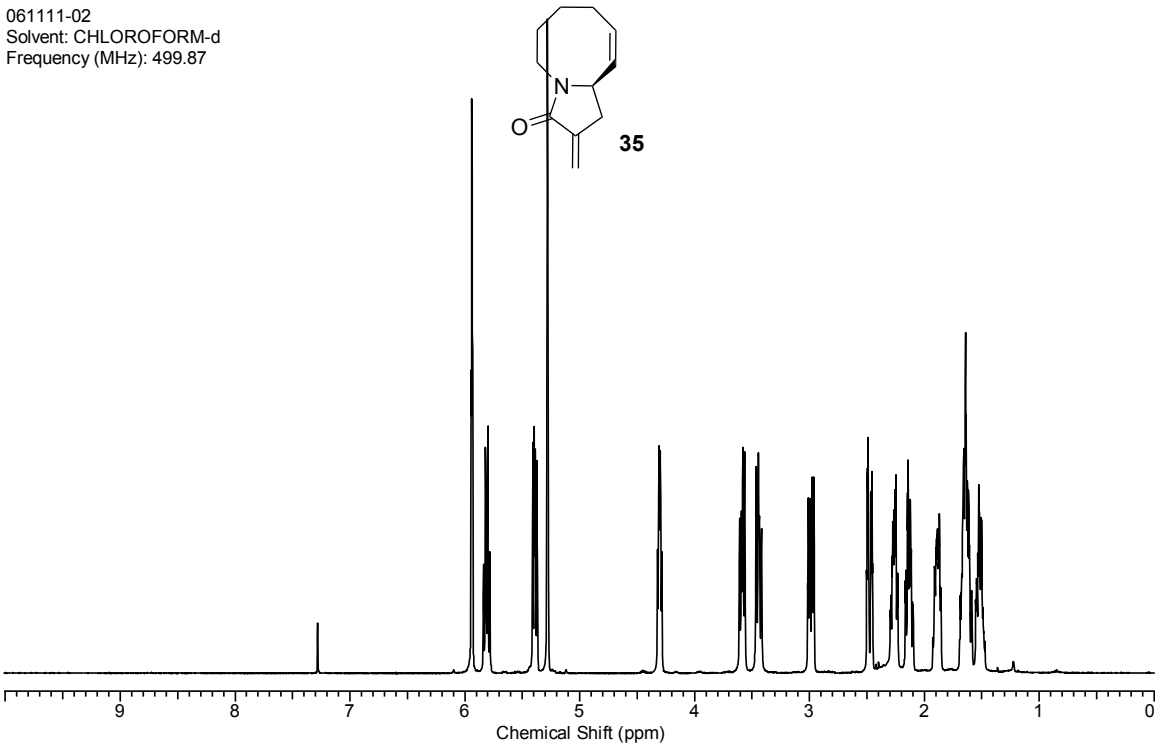


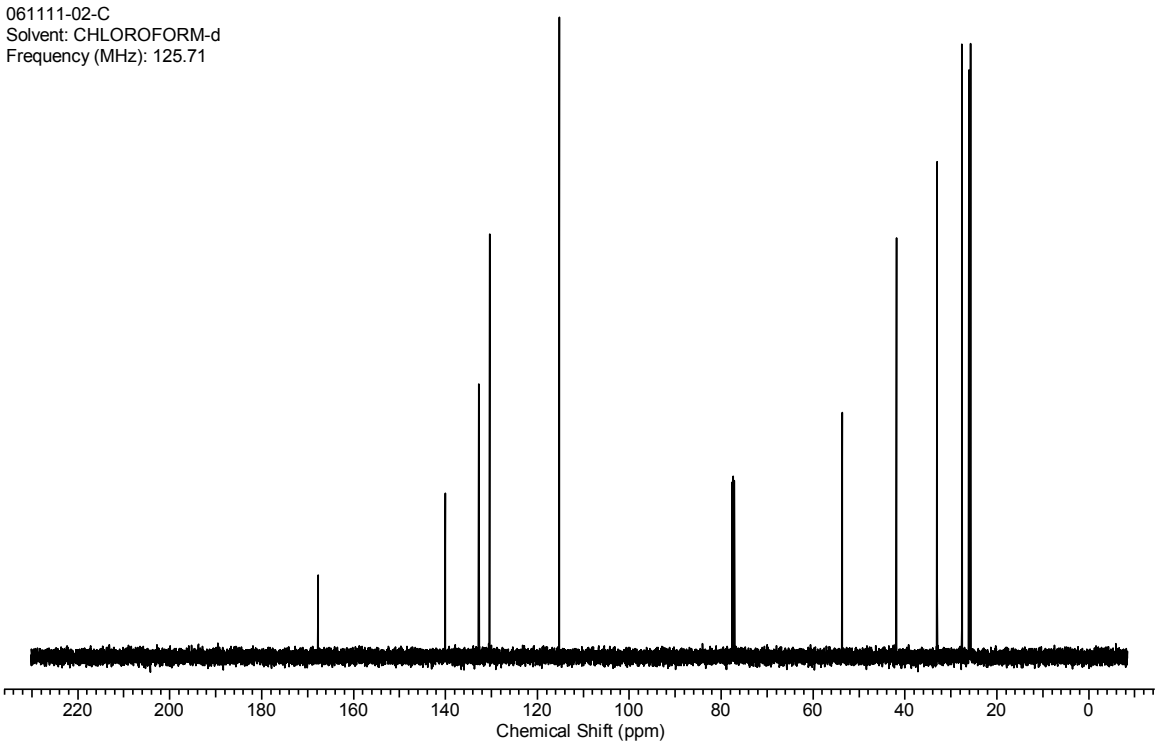

021913-07
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
O
NH
51
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


021913-08-C-1
Solvent: cdcl3
Frequency (MHz): 100.44
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

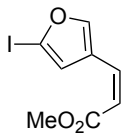

021313-05
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
O
N
52
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


021813-01-C
Solvent: cdcl3
Frequency (MHz): 100.44
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


061111-02
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87
N
O
35
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

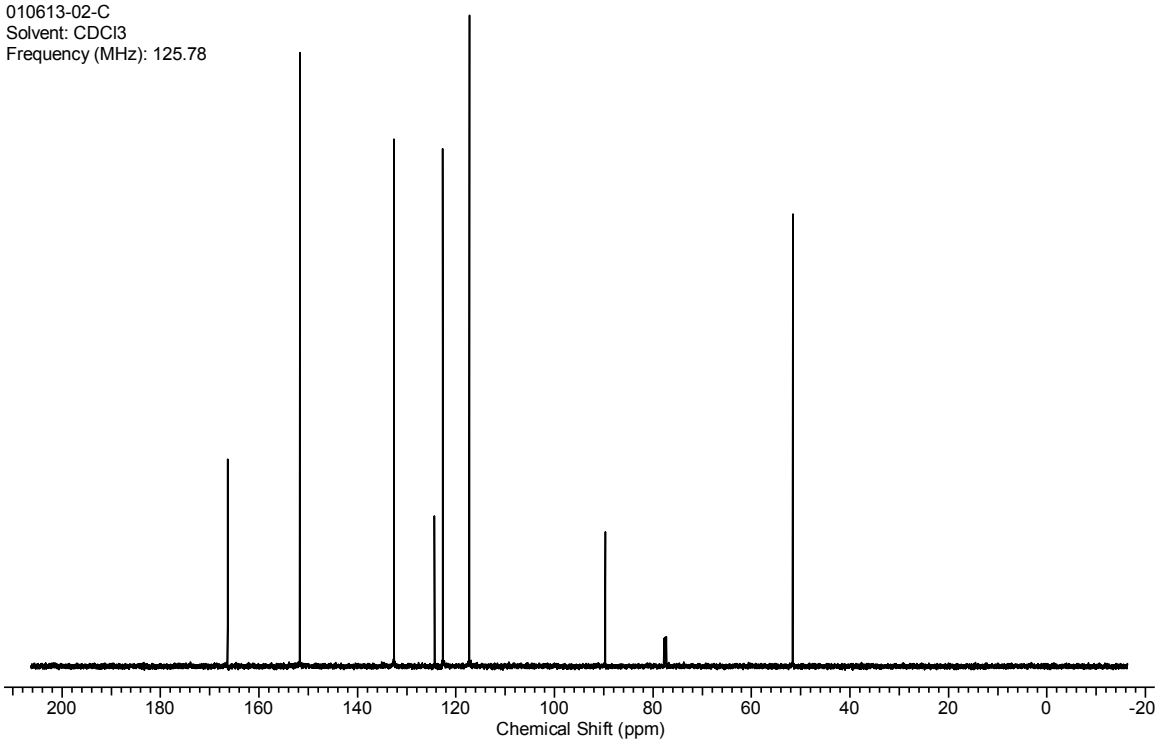

061111-02-C
Solvent: CHLOROFORM-d
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

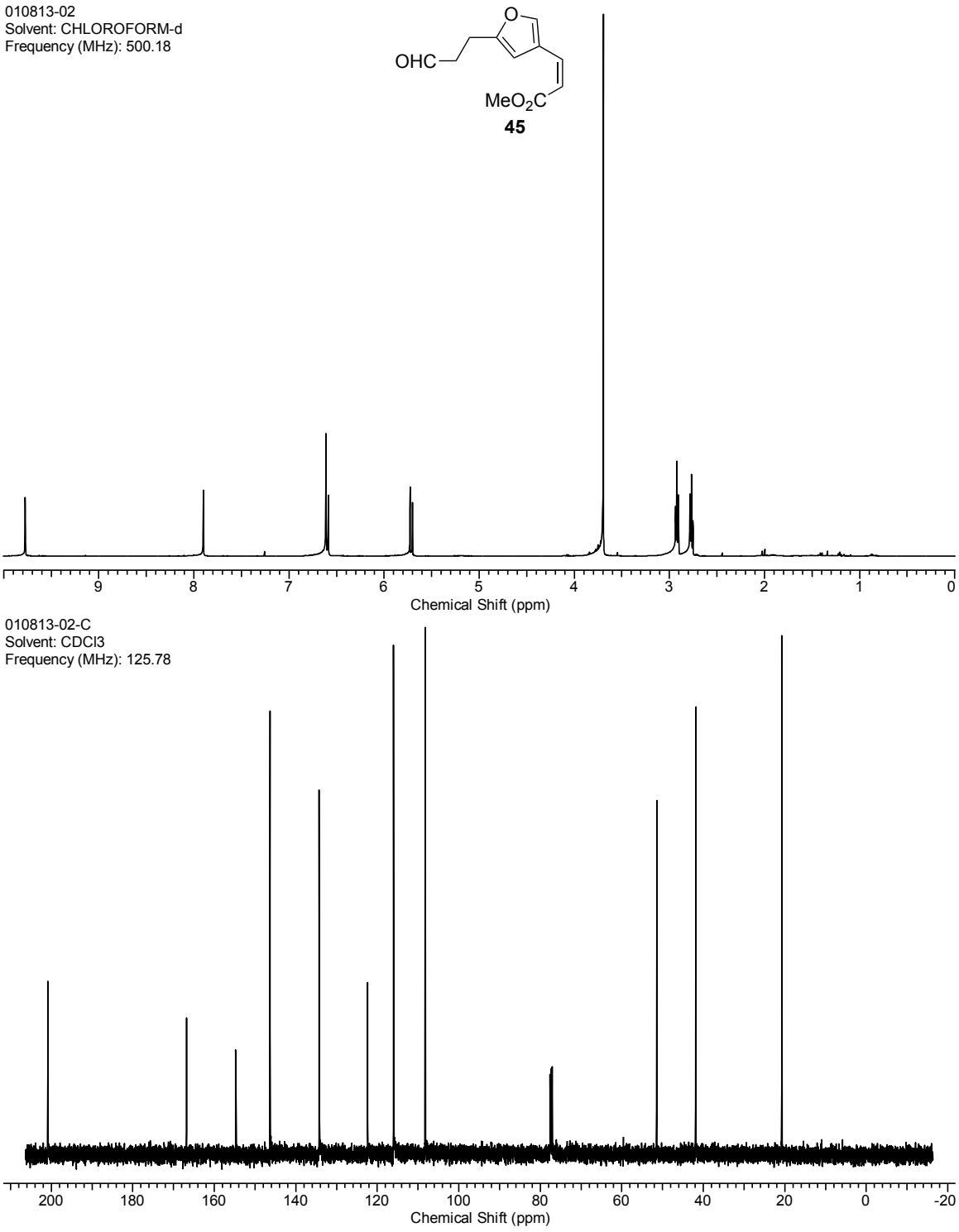
010613-02
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18



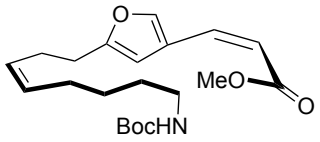
44

010613-02-C
Solvent: CDCl3
Frequency (MHz): 125.78

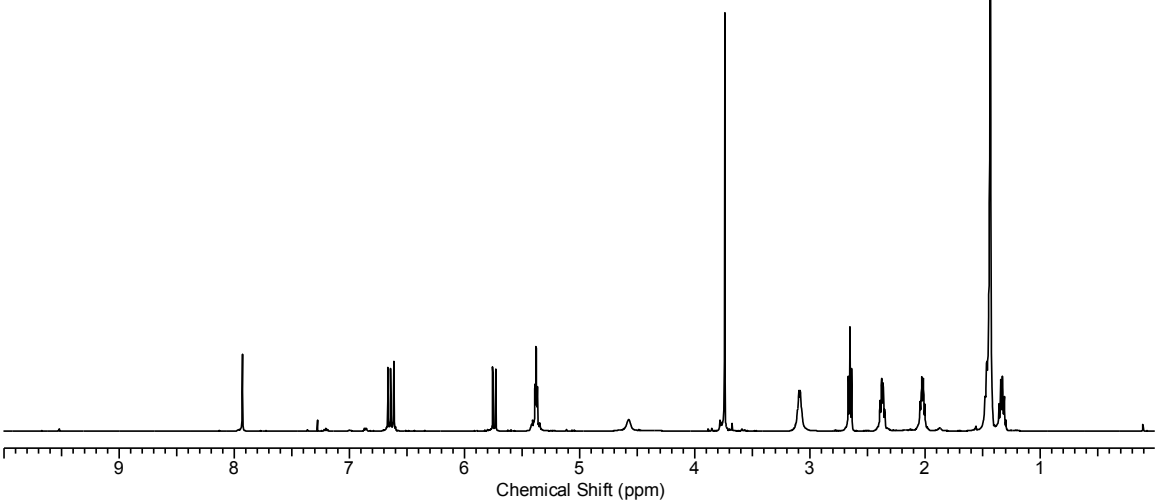



010813-02
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18
O
OHC
MeO2C
45
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
010813-02-C
Solvent: CDCl3
Frequency (MHz): 125.78
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

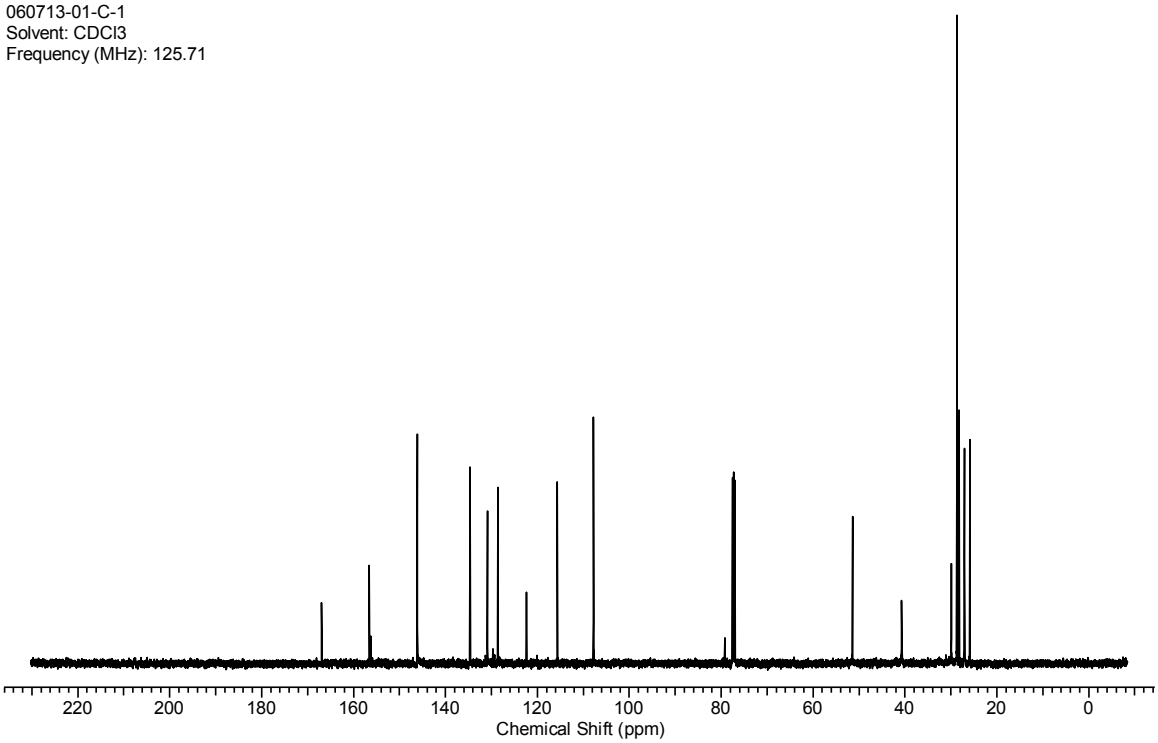
060713-01
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87

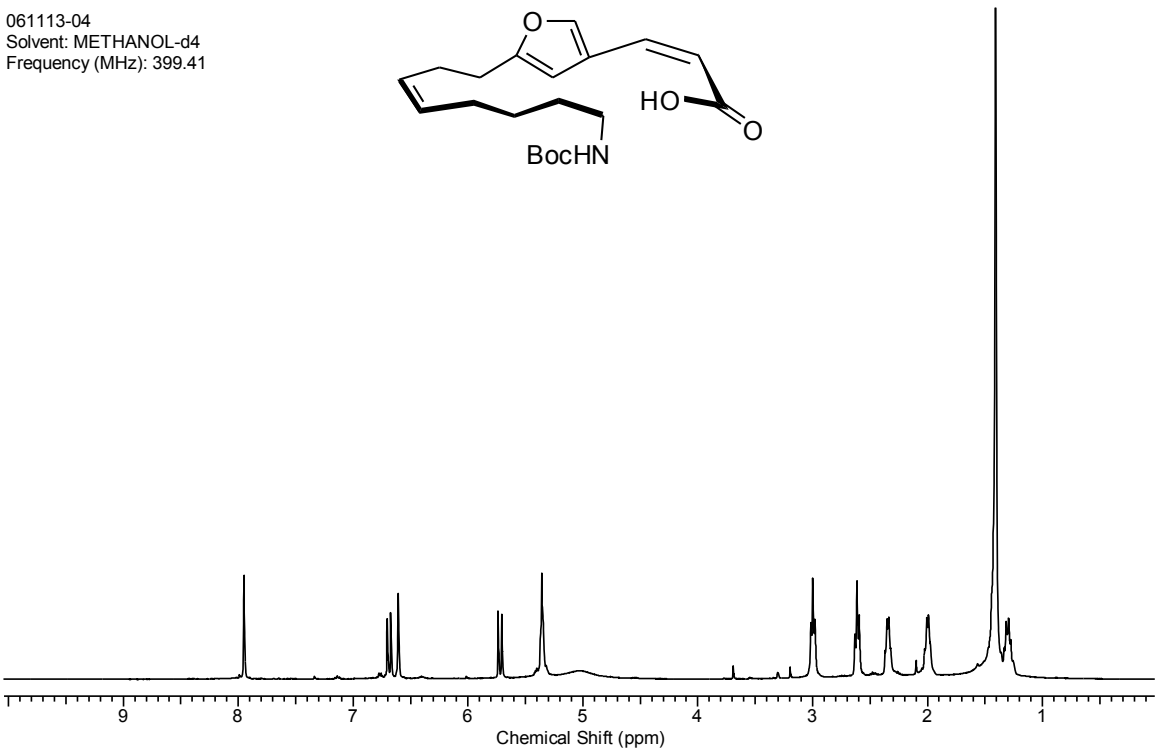


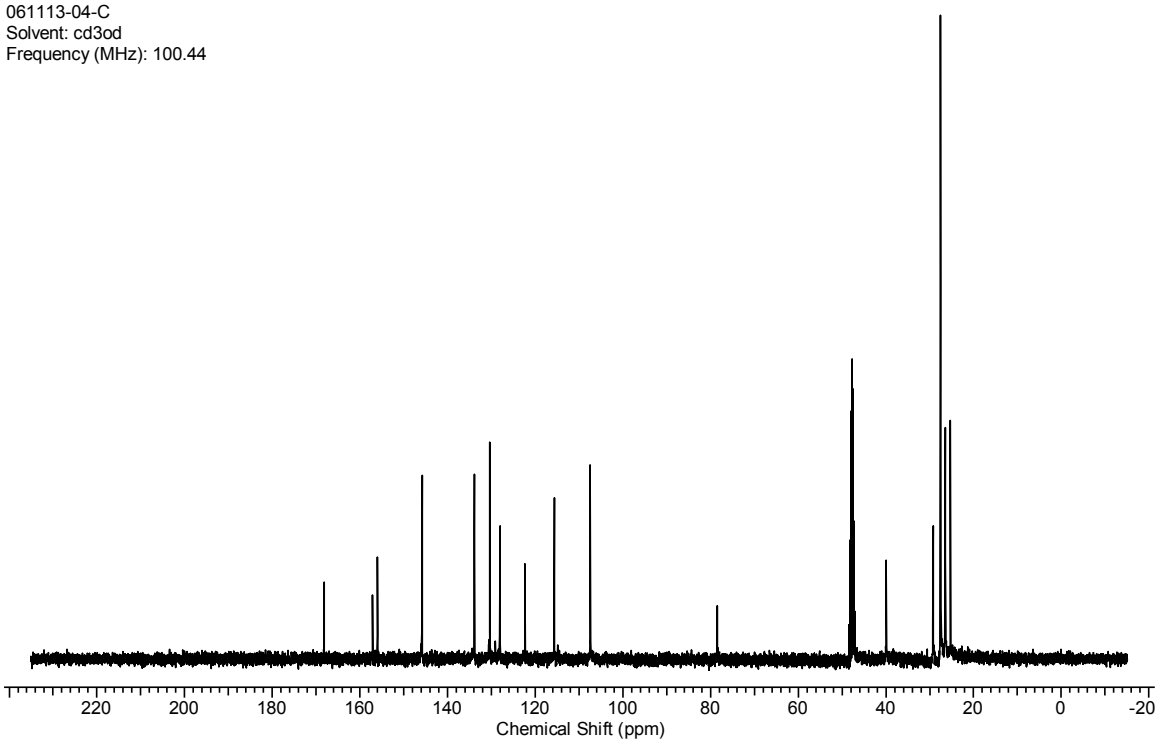
46

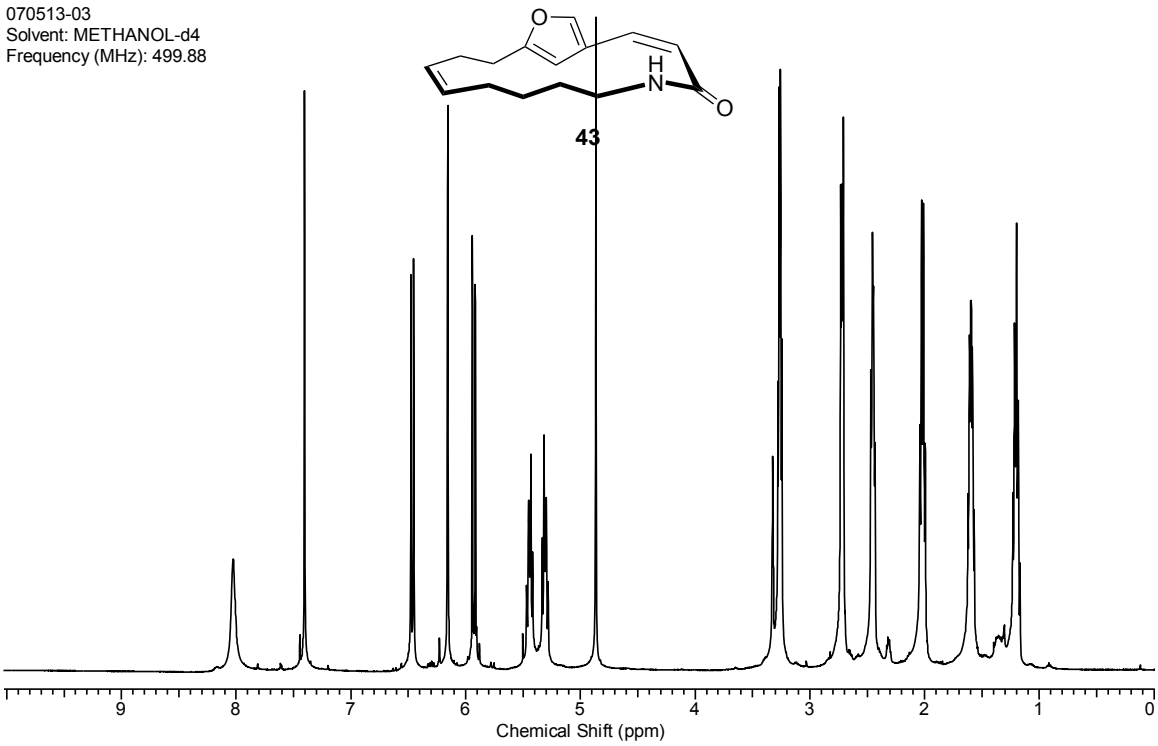


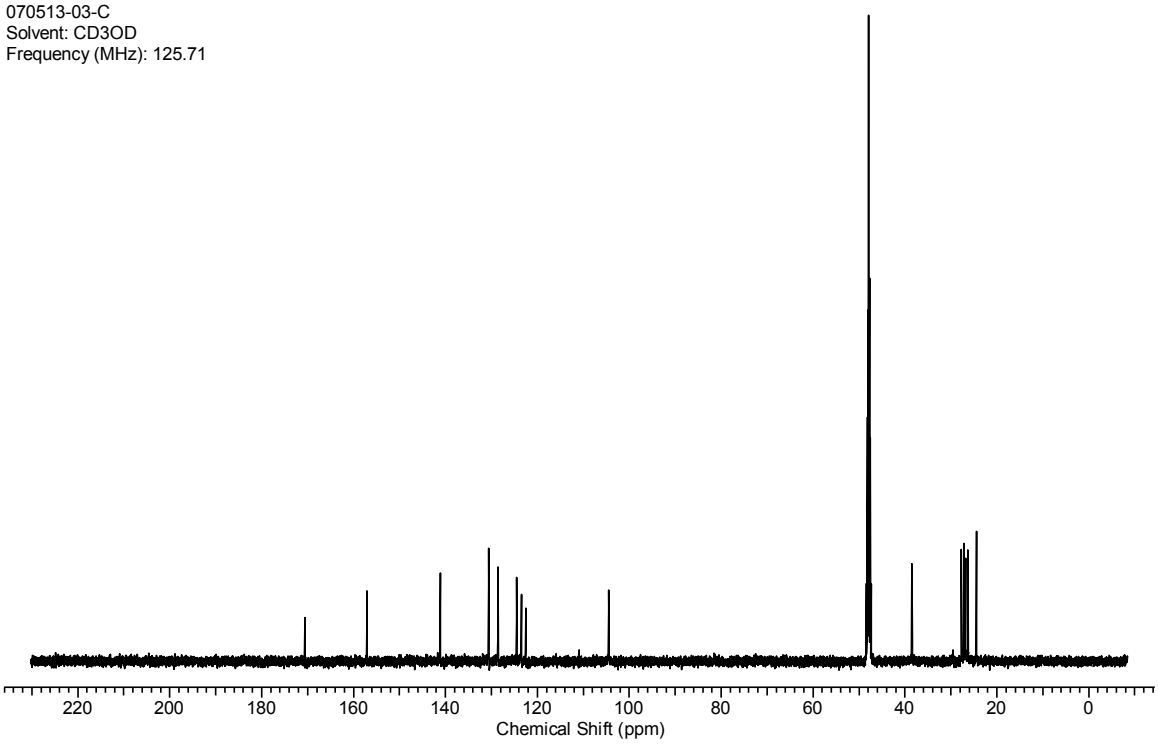
060713-01-C-1
Solvent: CDCl3
Frequency (MHz): 125.71

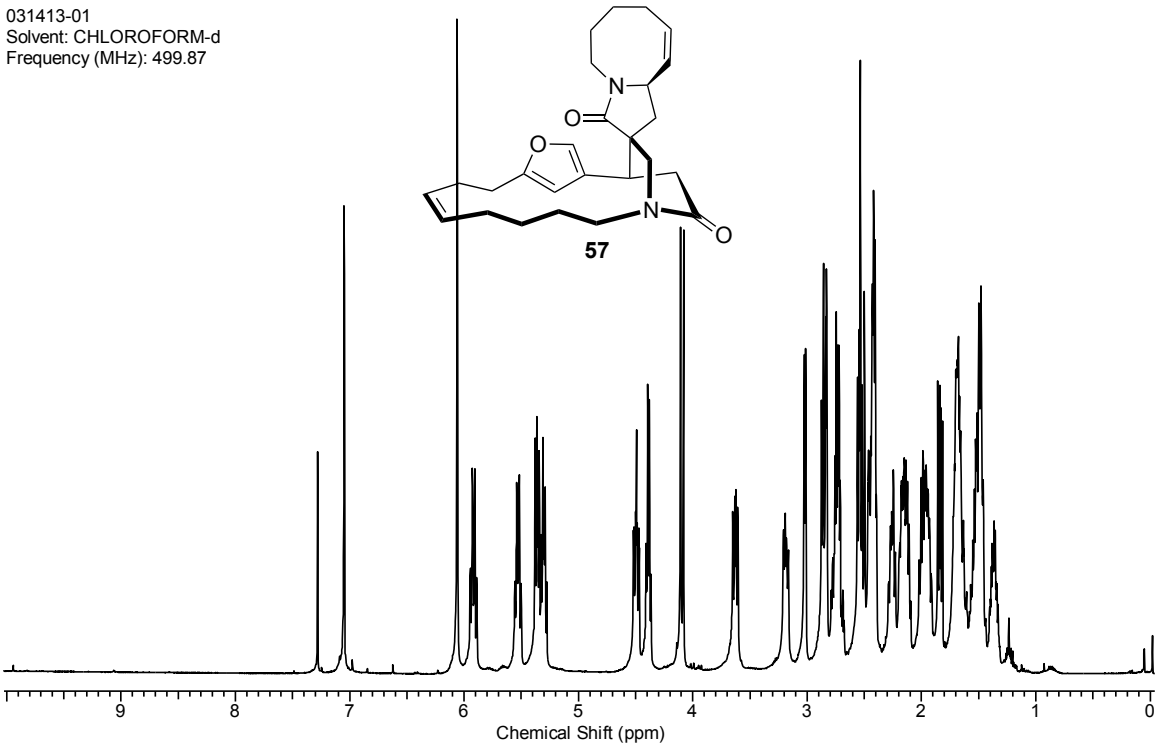


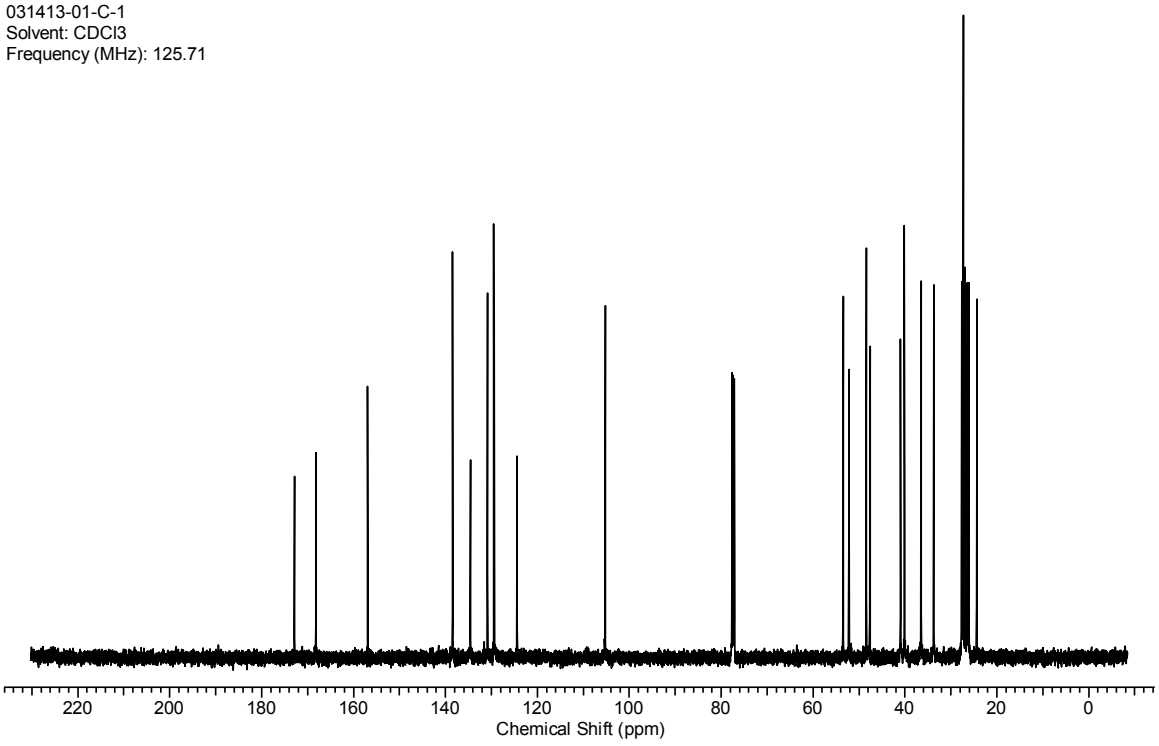

061113-04
Solvent: METHANOL-d4
Frequency (MHz): 399.41
O
HO
O
BocHN
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

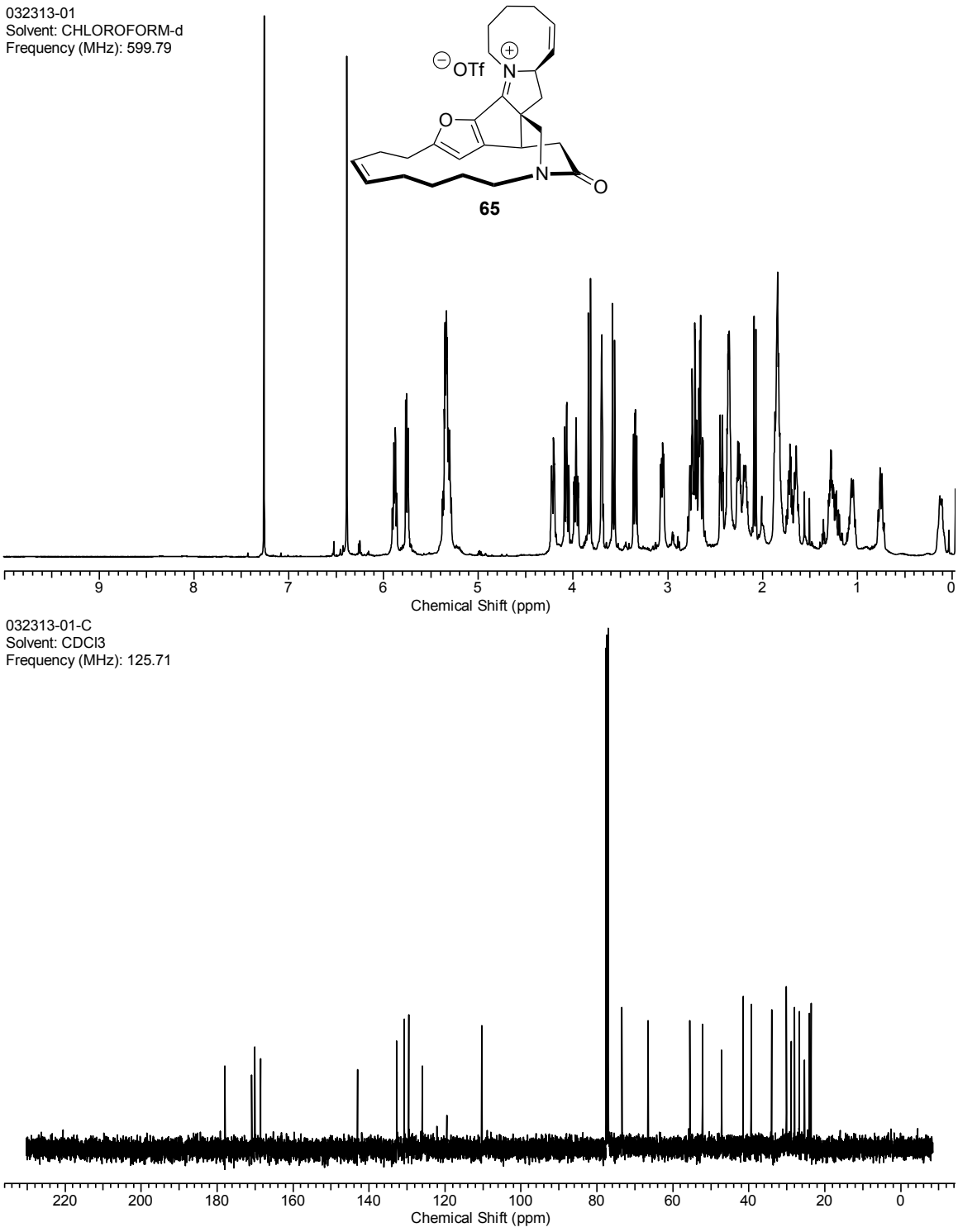

061113-04-C
Solvent: cd3od
Frequency (MHz): 100.44
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


070513-03
Solvent: METHANOL-d4
Frequency (MHz): 499.88
O
H
N
O
43
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

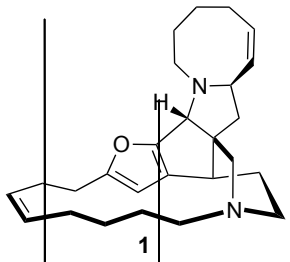

070513-03-C
Solvent: CD3OD
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


031413-01
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87
N
O
O
N
O
57
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

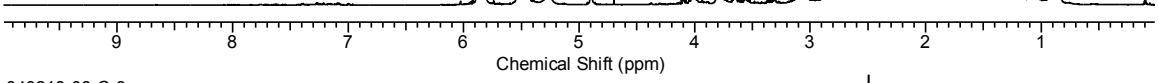

031413-01-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


032313-01
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
OTf
N
O
N
O
65
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
032313-01-C
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

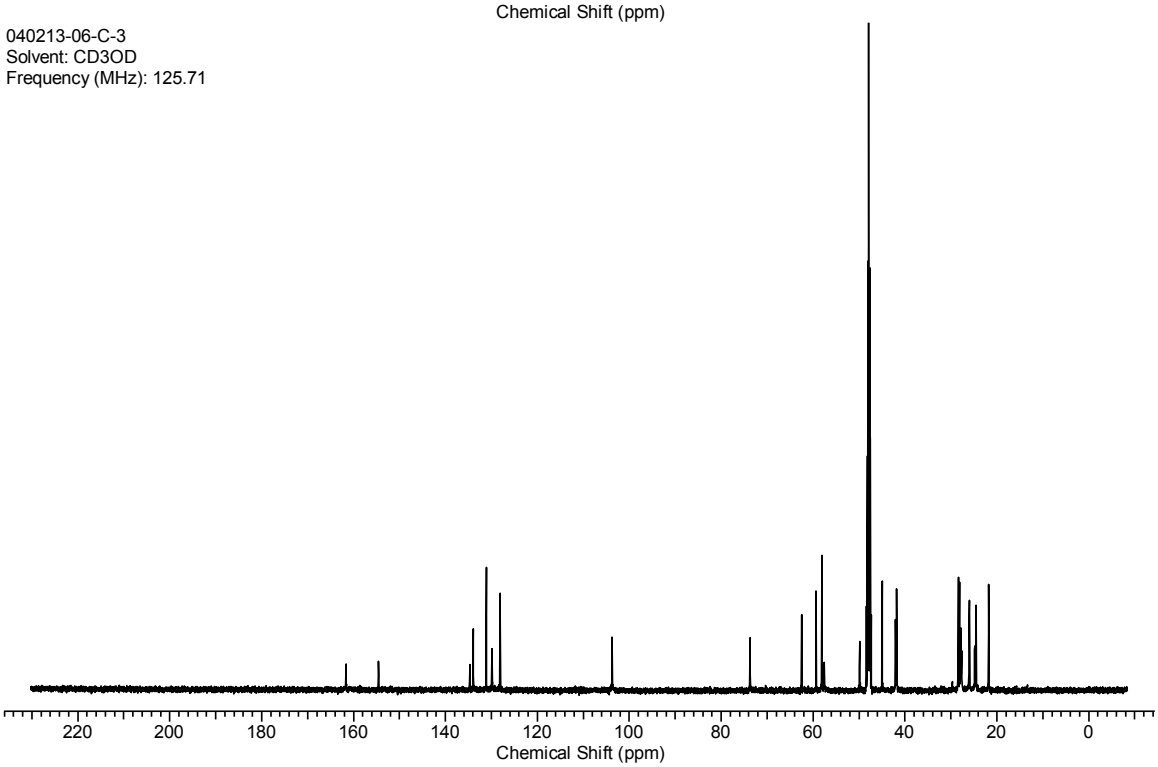
040213-06
Solvent: METHANOL-d4
Frequency (MHz): 599.79



1

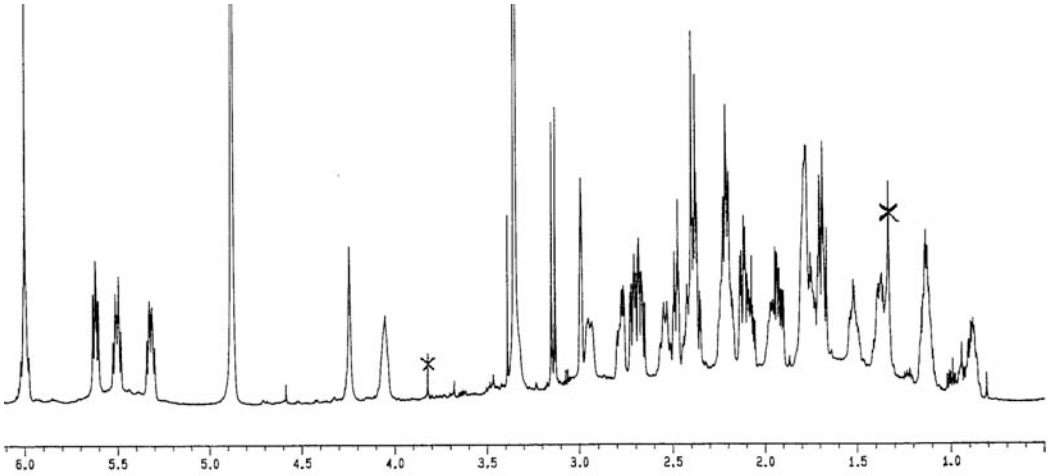


040213-06-C-3
Solvent: CD3OD
Frequency (MHz): 125.71



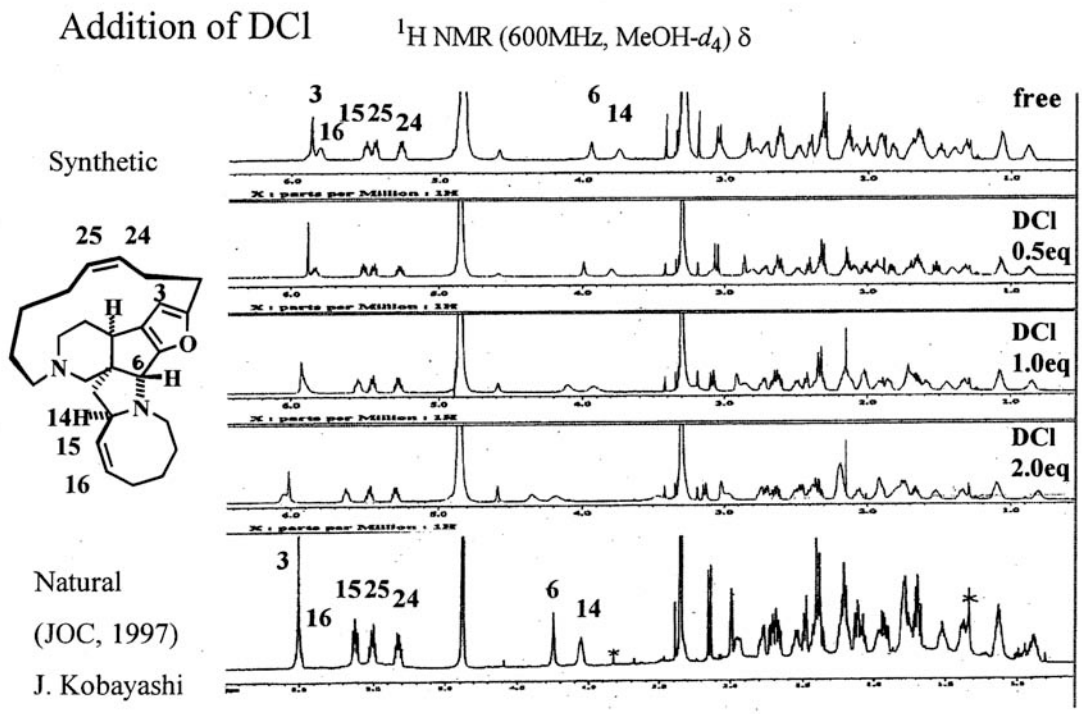
(−)-Nakadomarin A: ^{1}H NMR

Natural: Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236–9239.



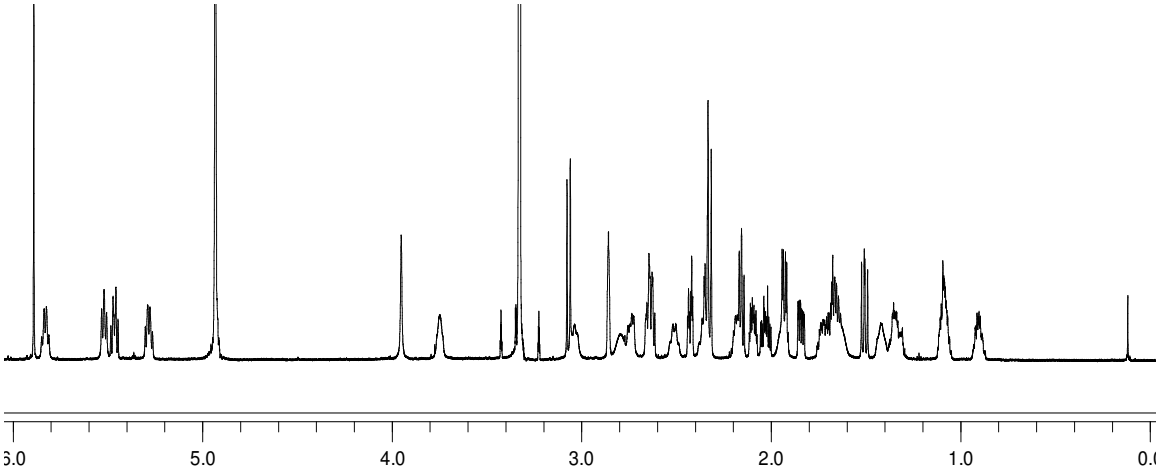
Influence of acid on the ^{1}H NMR spectrum of (−)-nakadomarin A.

Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484–7485.

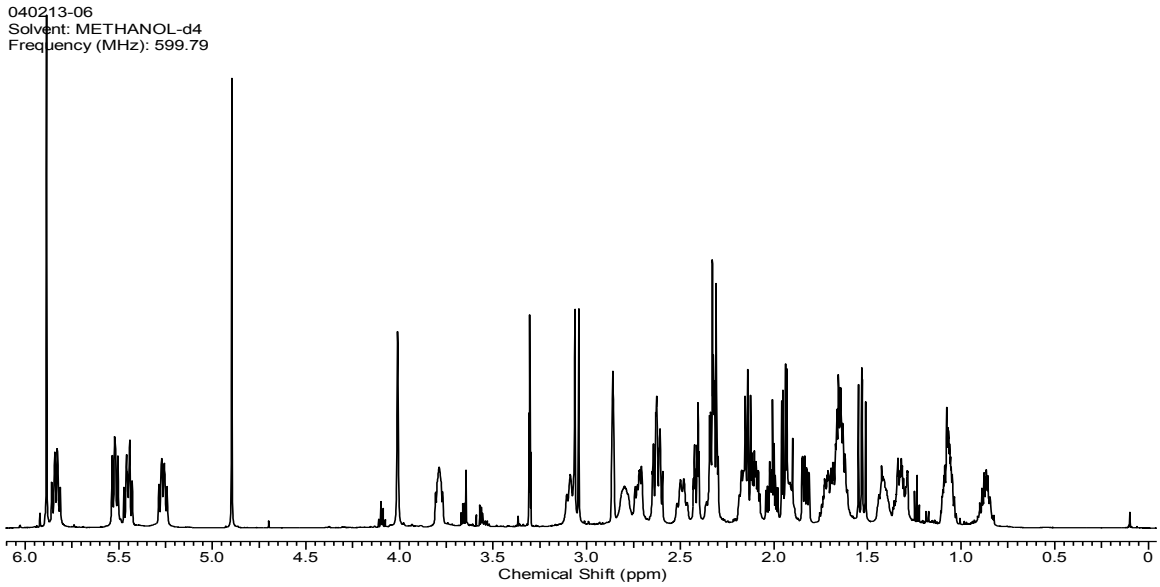


(–)-Nakadomarin A: ^{1}H NMR

Dixon: Jakubec, P.; Cockfield, D.; Dixon, D. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

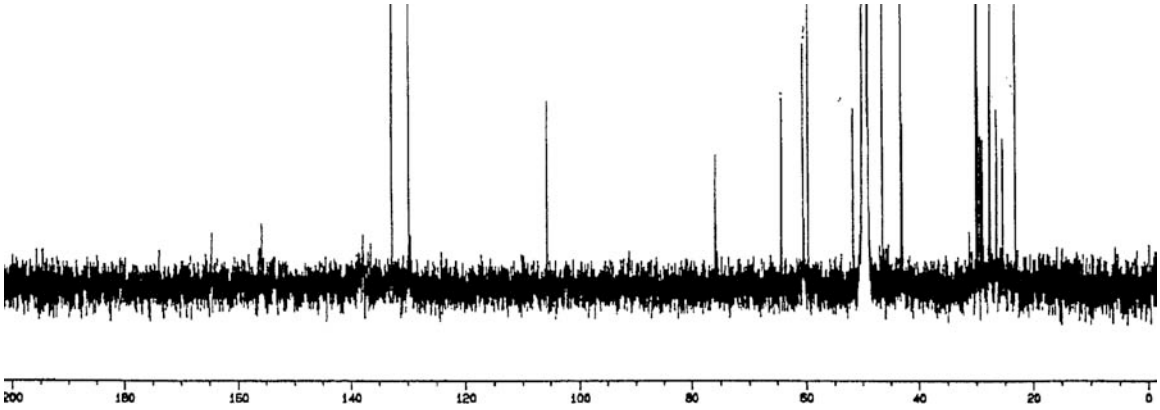


Synthetic

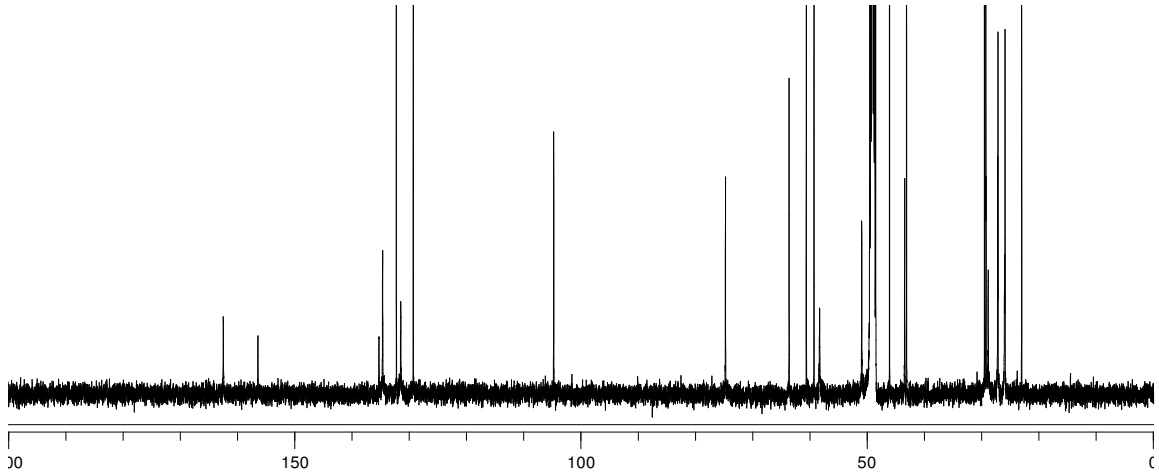


(–)-Nakadomarin A: ^{13}C NMR

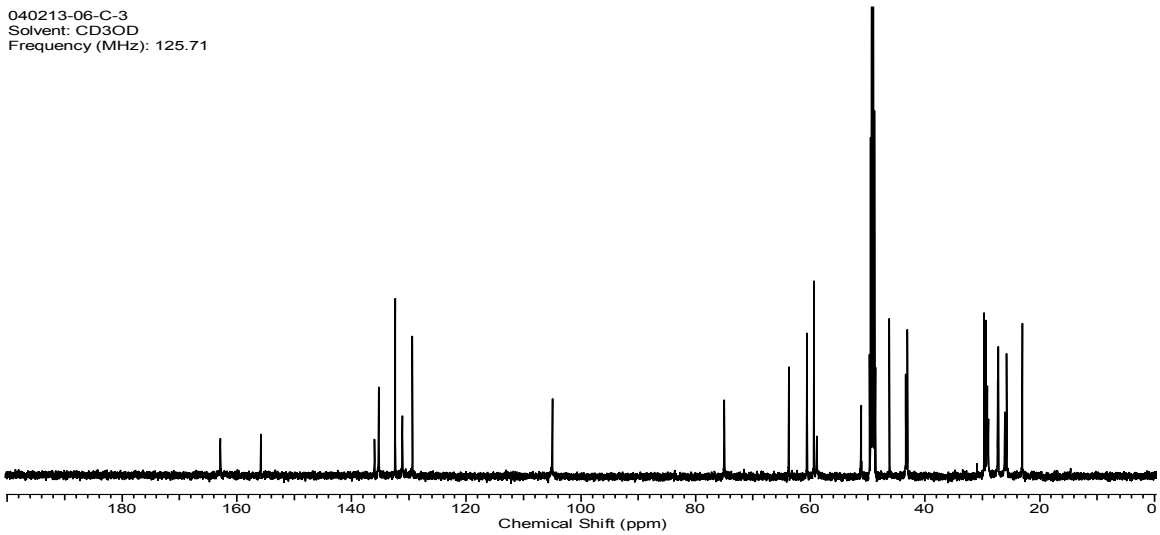
Natural: Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236–9239.



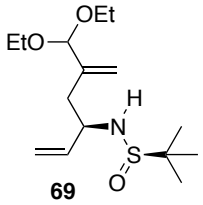
Dixon: Jakubec, P.; Cockfield, D.; Dixon, D. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.



Synthetic

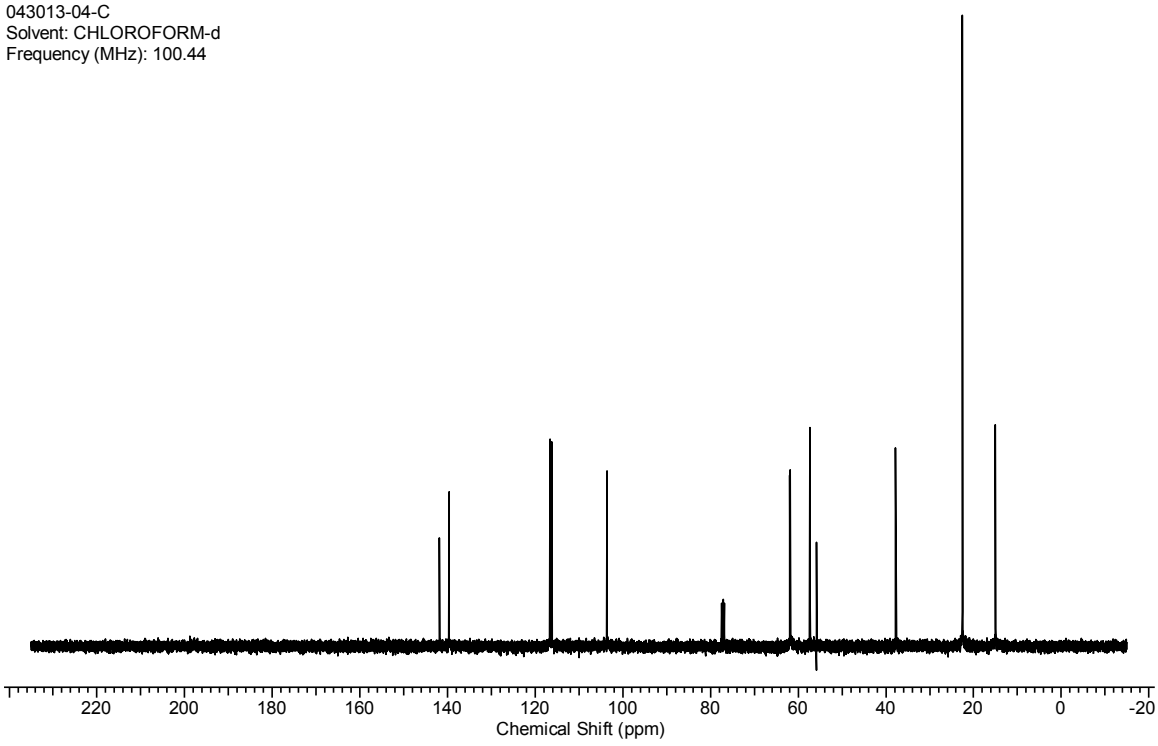


043013-04
Solvent: CHLOROFORM-d
Frequency (MHz): 500.18

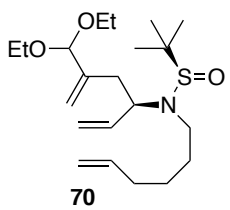


69

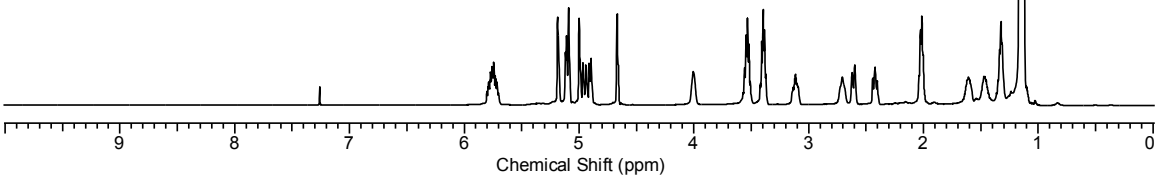
043013-04-C
Solvent: CHLOROFORM-d
Frequency (MHz): 100.44



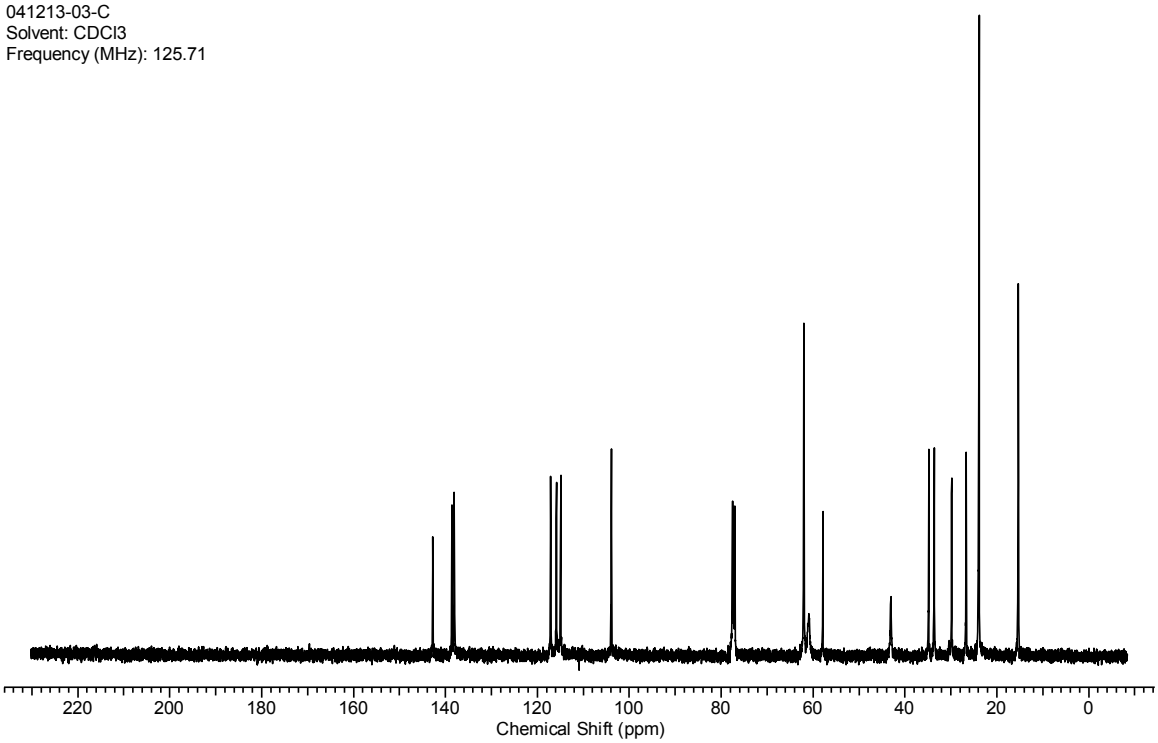
041213-03
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79

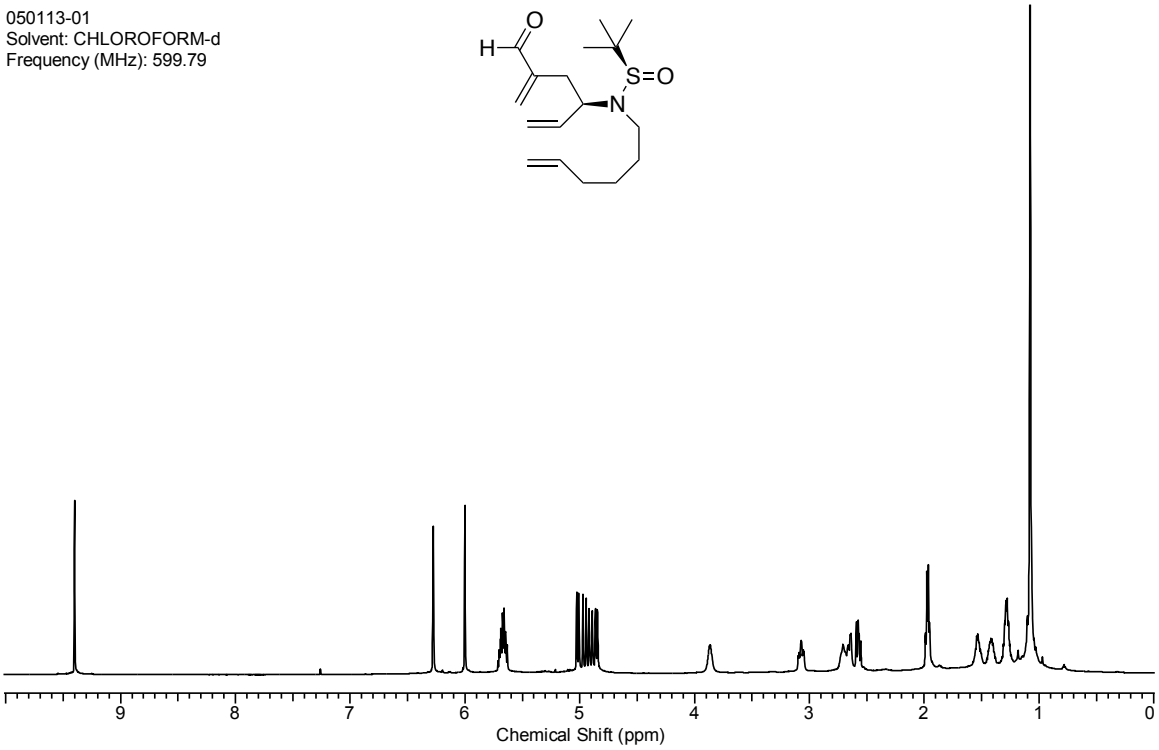


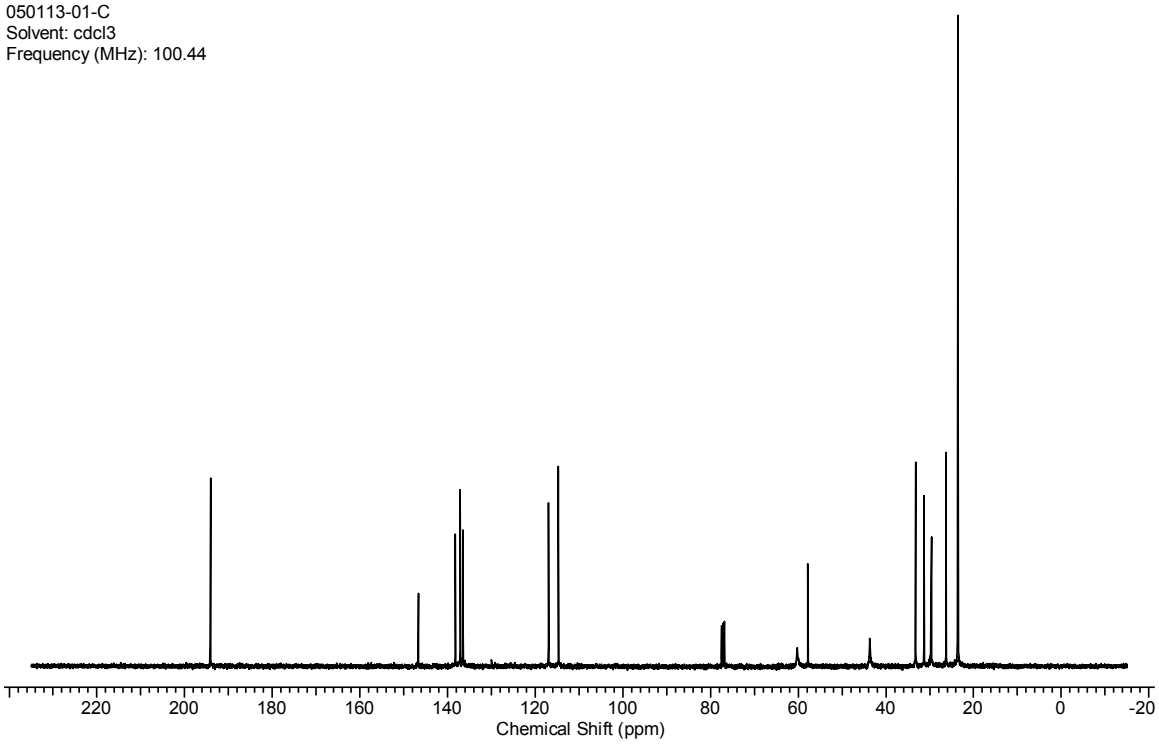
70

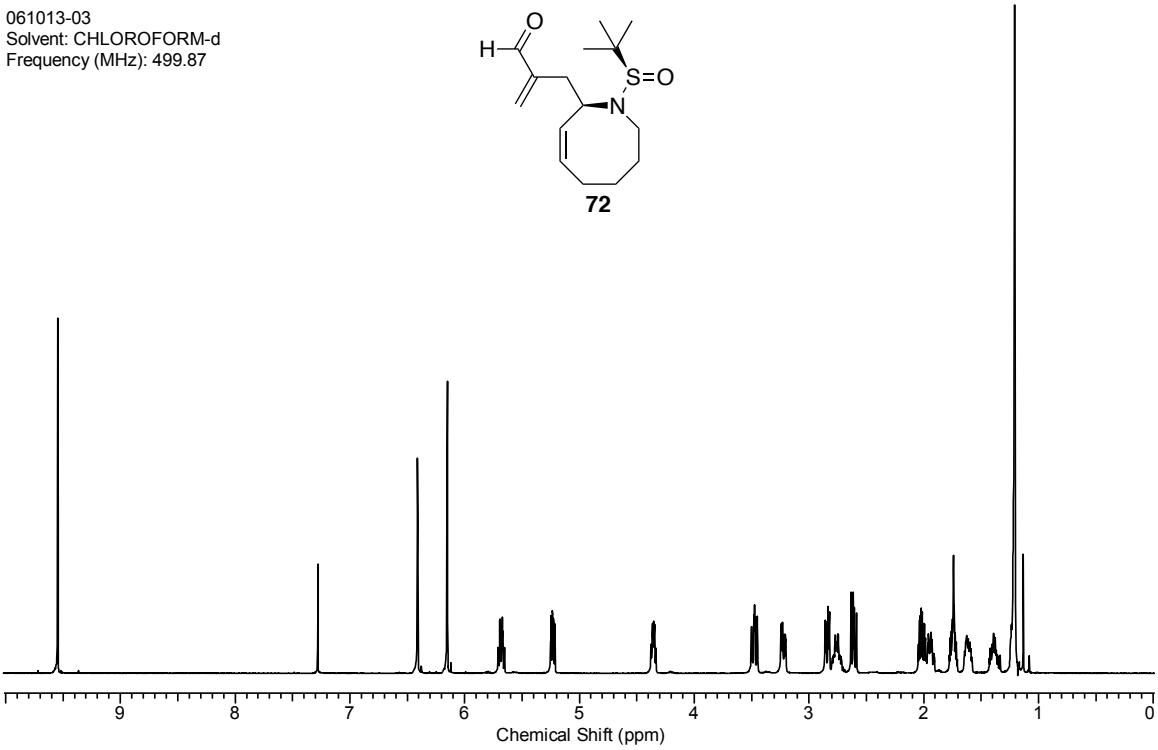


041213-03-C
Solvent: CDCl3
Frequency (MHz): 125.71

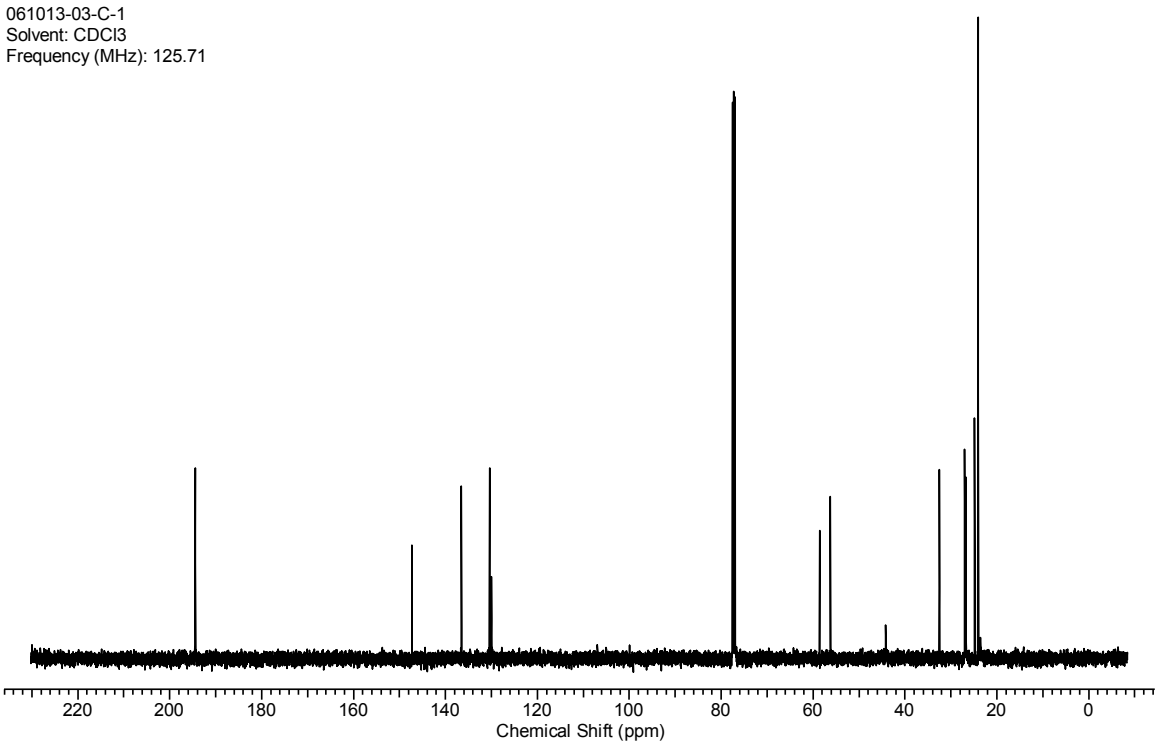


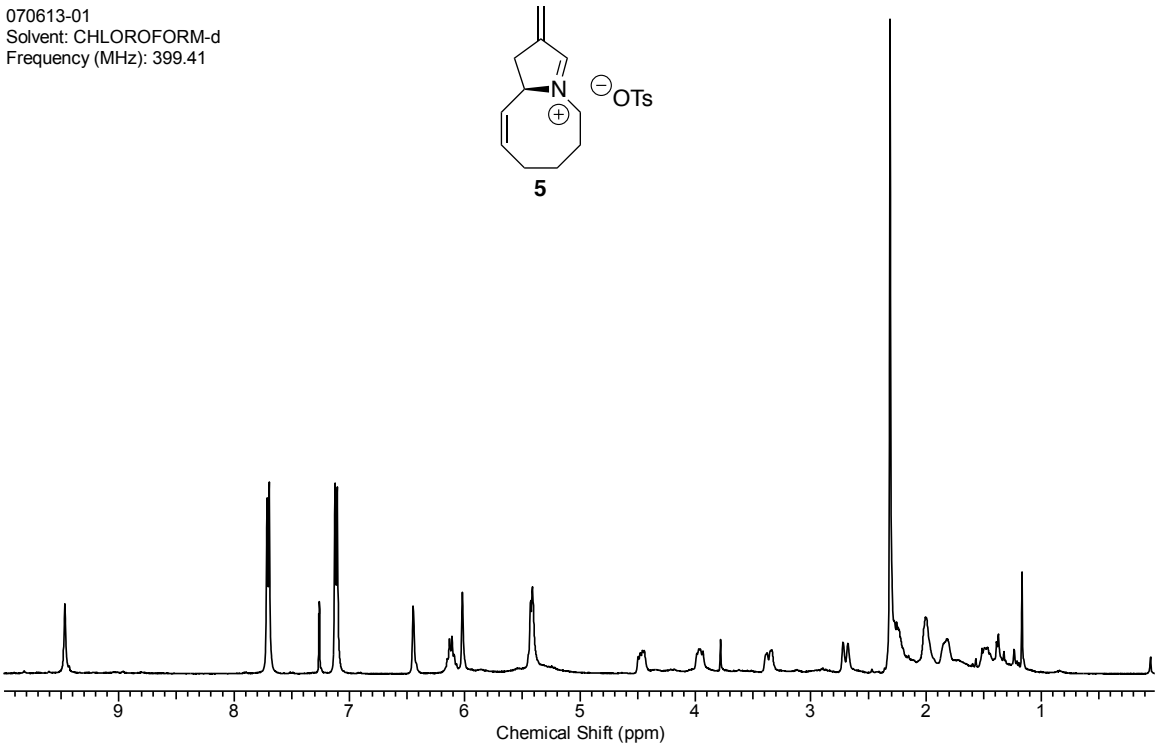

050113-01
Solvent: CHLOROFORM-d
Frequency (MHz): 599.79
O
H
S=O
N
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


050113-01-C
Solvent: cdcl3
Frequency (MHz): 100.44
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

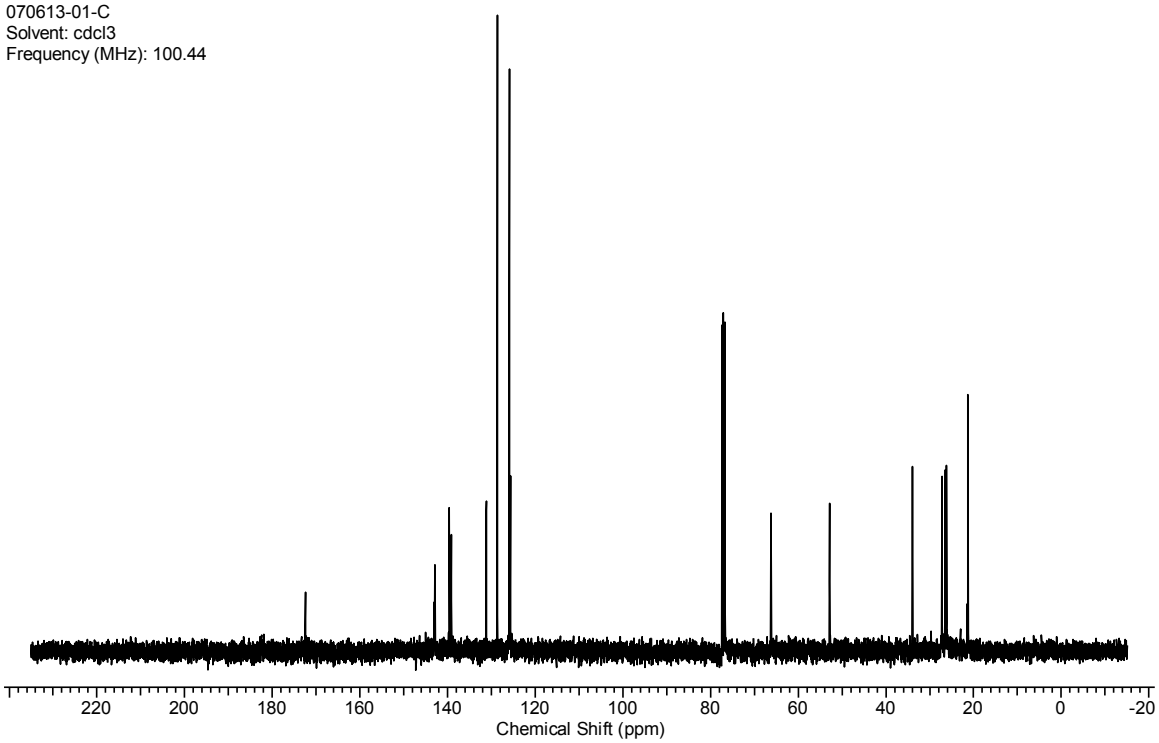

061013-03
Solvent: CHLOROFORM-d
Frequency (MHz): 499.87
O
H
S=O
N
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

72


061013-03-C-1
Solvent: CDCl3
Frequency (MHz): 125.71
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


070613-01
Solvent: CHLOROFORM-d
Frequency (MHz): 399.41
N
OTs
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

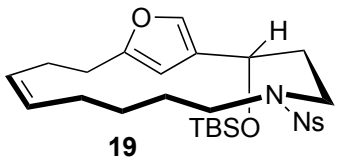
5


070613-01-C
Solvent: cdcl3
Frequency (MHz): 100.44
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

Appendix III

X-ray Structure Data

(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-5-((2-nitrophenyl)sulfonyl)-15-oxa-5-azabicyclo[12.2.1]heptadeca-1(16),10,14(17)-triene (**19**)



19

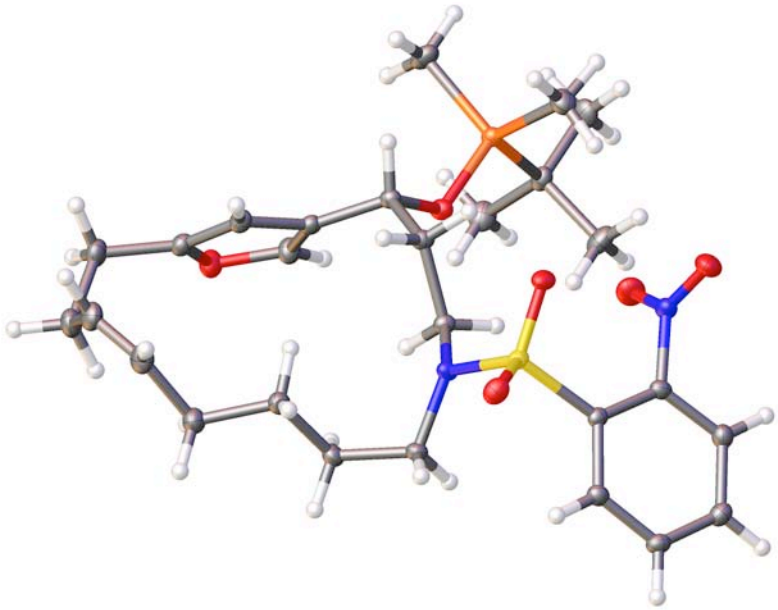


Figure 1. X-ray Structure of **19**.

X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.74 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 1. Experimental details

	cbc002
Crystal data	
Chemical formula	$C_{27}H_{40}N_2O_6SSi$
M_r	548.76
Crystal system, space group	Orthorhombic, $p2_12_12_1$
Temperature (K)	100
a, b, c (Å)	8.3473 (4), 16.1064 (7), 21.0353 (9)
V (Å^3)	2828.1 (2)
Z	4
Radiation type	Mo $K\alpha$

Table 1 (Continued).

μ (mm^{-1})	0.20
Crystal size (mm)	0.32 × 0.24 × 0.18
Data collection	
Diffractometer	CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.939, 0.965
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	108710, 7335, 7178
R_{int}	0.034
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.024, 0.065, 1.07
No. of reflections	7335
No. of parameters	339
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.32, -0.26
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.00 (4)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL*.

Table 2. Geometric parameters (Å, º)

S1—O3	1.4333 (8)	C11—H11A	0.9900
S1—O4	1.4379 (8)	C11—H11B	0.9900
S1—N1	1.6236 (9)	C12—H12A	0.9900
S1—C16	1.7881 (10)	C12—H12B	0.9900
Si1—O2	1.6572 (8)	C13—C14	1.5293 (14)
Si1—C23	1.8633 (13)	C13—H13A	0.9900
Si1—C22	1.8707 (12)	C13—H13B	0.9900
Si1—C24	1.8809 (11)	C14—C15	1.5324 (13)
O1—C1	1.3747 (14)	C14—H14A	0.9900

Table 2 (Continued).

O1—C4	1.3759 (14)	C14—H14B	0.9900
O2—C15	1.4289 (12)	C15—H15	1.0000
O5—N2	1.2171 (14)	C16—C17	1.3939 (15)
O6—N2	1.2260 (13)	C16—C21	1.3996 (14)
N1—C13	1.4907 (12)	C17—C18	1.3871 (15)
N1—C12	1.4913 (13)	C18—C19	1.3919 (15)
N2—C17	1.4788 (13)	C18—H18	0.9500
C1—C2	1.3529 (15)	C19—C20	1.3890 (16)
C1—H1	0.9500	C19—H19	0.9500
C2—C3	1.4433 (14)	C20—C21	1.3914 (15)
C2—C15	1.5018 (15)	C20—H20	0.9500
C3—C4	1.3577 (16)	C21—H21	0.9500
C3—H3	0.9500	C22—H22A	0.9800
C4—C5	1.4948 (16)	C22—H22B	0.9800
C5—C6	1.5420 (18)	C22—H22C	0.9800
C5—H5A	0.9900	C23—H23A	0.9800
C5—H5B	0.9900	C23—H23B	0.9800
C6—C7	1.5024 (18)	C23—H23C	0.9800
C6—H6A	0.9900	C24—C26	1.5346 (17)
C6—H6B	0.9900	C24—C25	1.5389 (15)
C7—C8	1.3294 (17)	C24—C27	1.5426 (16)
C7—H7	0.9500	C25—H25A	0.9800
C8—C9	1.4992 (17)	C25—H25B	0.9800
C8—H8	0.9500	C25—H25C	0.9800
C9—C10	1.5339 (16)	C26—H26A	0.9800
C9—H9A	0.9900	C26—H26B	0.9800
C9—H9B	0.9900	C26—H26C	0.9800
C10—C11	1.5195 (15)	C27—H27A	0.9800
C10—H10A	0.9900	C27—H27B	0.9800
C10—H10B	0.9900	C27—H27C	0.9800
C11—C12	1.5186 (15)		
O3—S1—O4	119.72 (5)	H12A—C12—H12B	107.8
O3—S1—N1	108.03 (5)	N1—C13—C14	112.22 (8)
O4—S1—N1	108.27 (4)	N1—C13—H13A	109.2
O3—S1—C16	105.10 (5)	C14—C13—H13A	109.2

Table 2 (Continued).

O4—S1—C16	106.79 (5)	N1—C13—H13B	109.2
N1—S1—C16	108.49 (5)	C14—C13—H13B	109.2
O2—Si1—C23	109.42 (5)	H13A—C13—H13B	107.9
O2—Si1—C22	109.19 (5)	C13—C14—C15	112.87 (8)
C23—Si1—C22	109.84 (6)	C13—C14—H14A	109.0
O2—Si1—C24	105.06 (5)	C15—C14—H14A	109.0
C23—Si1—C24	111.71 (5)	C13—C14—H14B	109.0
C22—Si1—C24	111.47 (5)	C15—C14—H14B	109.0
C1—O1—C4	106.67 (9)	H14A—C14—H14B	107.8
C15—O2—Si1	121.78 (7)	O2—C15—C2	108.69 (8)
C13—N1—C12	117.10 (8)	O2—C15—C14	109.82 (8)
C13—N1—S1	119.03 (7)	C2—C15—C14	114.27 (9)
C12—N1—S1	114.83 (6)	O2—C15—H15	108.0
O5—N2—O6	125.67 (10)	C2—C15—H15	108.0
O5—N2—C17	117.44 (9)	C14—C15—H15	108.0
O6—N2—C17	116.76 (9)	C17—C16—C21	117.71 (9)
C2—C1—O1	110.87 (10)	C17—C16—S1	124.47 (8)
C2—C1—H1	124.6	C21—C16—S1	117.78 (8)
O1—C1—H1	124.6	C18—C17—C16	122.34 (10)
C1—C2—C3	105.72 (10)	C18—C17—N2	115.35 (9)
C1—C2—C15	126.38 (10)	C16—C17—N2	122.31 (9)
C3—C2—C15	127.70 (10)	C17—C18—C19	118.81 (10)
C4—C3—C2	106.99 (9)	C17—C18—H18	120.6
C4—C3—H3	126.5	C19—C18—H18	120.6
C2—C3—H3	126.5	C20—C19—C18	120.23 (10)
C3—C4—O1	109.76 (9)	C20—C19—H19	119.9
C3—C4—C5	134.80 (11)	C18—C19—H19	119.9
O1—C4—C5	115.43 (10)	C19—C20—C21	120.10 (10)
C4—C5—C6	114.43 (9)	C19—C20—H20	120.0
C4—C5—H5A	108.7	C21—C20—H20	120.0
C6—C5—H5A	108.7	C20—C21—C16	120.76 (10)
C4—C5—H5B	108.7	C20—C21—H21	119.6
C6—C5—H5B	108.7	C16—C21—H21	119.6
H5A—C5—H5B	107.6	Si1—C22—H22A	109.5
C7—C6—C5	113.56 (11)	Si1—C22—H22B	109.5
C7—C6—H6A	108.9	H22A—C22—H22B	109.5

Table 2 (Continued).

C5—C6—H6A	108.9	Si1—C22—H22C	109.5
C7—C6—H6B	108.9	H22A—C22—H22C	109.5
C5—C6—H6B	108.9	H22B—C22—H22C	109.5
H6A—C6—H6B	107.7	Si1—C23—H23A	109.5
C8—C7—C6	127.23 (12)	Si1—C23—H23B	109.5
C8—C7—H7	116.4	H23A—C23—H23B	109.5
C6—C7—H7	116.4	Si1—C23—H23C	109.5
C7—C8—C9	126.90 (12)	H23A—C23—H23C	109.5
C7—C8—H8	116.5	H23B—C23—H23C	109.5
C9—C8—H8	116.5	C26—C24—C25	108.66 (10)
C8—C9—C10	111.12 (10)	C26—C24—C27	108.96 (9)
C8—C9—H9A	109.4	C25—C24—C27	108.97 (10)
C10—C9—H9A	109.4	C26—C24—Si1	110.38 (8)
C8—C9—H9B	109.4	C25—C24—Si1	110.14 (7)
C10—C9—H9B	109.4	C27—C24—Si1	109.70 (8)
H9A—C9—H9B	108.0	C24—C25—H25A	109.5
C11—C10—C9	111.64 (9)	C24—C25—H25B	109.5
C11—C10—H10A	109.3	H25A—C25—H25B	109.5
C9—C10—H10A	109.3	C24—C25—H25C	109.5
C11—C10—H10B	109.3	H25A—C25—H25C	109.5
C9—C10—H10B	109.3	H25B—C25—H25C	109.5
H10A—C10—H10B	108.0	C24—C26—H26A	109.5
C12—C11—C10	113.80 (9)	C24—C26—H26B	109.5
C12—C11—H11A	108.8	H26A—C26—H26B	109.5
C10—C11—H11A	108.8	C24—C26—H26C	109.5
C12—C11—H11B	108.8	H26A—C26—H26C	109.5
C10—C11—H11B	108.8	H26B—C26—H26C	109.5
H11A—C11—H11B	107.7	C24—C27—H27A	109.5
N1—C12—C11	113.09 (8)	C24—C27—H27B	109.5
N1—C12—H12A	109.0	H27A—C27—H27B	109.5
C11—C12—H12A	109.0	C24—C27—H27C	109.5
N1—C12—H12B	109.0	H27A—C27—H27C	109.5
C11—C12—H12B	109.0	H27B—C27—H27C	109.5
C23—Si1—O2—C15	65.18 (9)	C3—C2—C15—O2	-177.03 (10)
C22—Si1—O2—C15	-55.07 (9)	C1—C2—C15—C14	-126.00 (11)

Table 2 (Continued).

C24—Si1—O2—C15	-174.74 (7)	C3—C2—C15—C14	59.93 (14)
O3—S1—N1—C13	162.21 (8)	C13—C14—C15—O2	-50.92 (12)
O4—S1—N1—C13	31.18 (9)	C13—C14—C15—C2	71.50 (11)
C16—S1—N1—C13	-84.36 (8)	O3—S1—C16—C17	-145.34 (9)
O3—S1—N1—C12	-51.61 (9)	O4—S1—C16—C17	-17.20 (10)
O4—S1—N1—C12	177.36 (7)	N1—S1—C16—C17	99.30 (9)
C16—S1—N1—C12	61.83 (9)	O3—S1—C16—C21	32.33 (9)
C4—O1—C1—C2	0.35 (12)	O4—S1—C16—C21	160.48 (8)
O1—C1—C2—C3	-0.06 (13)	N1—S1—C16—C21	-83.03 (9)
O1—C1—C2—C15	-175.19 (9)	C21—C16—C17—C18	-0.42 (15)
C1—C2—C3—C4	-0.25 (12)	S1—C16—C17—C18	177.25 (8)
C15—C2—C3—C4	174.79 (10)	C21—C16—C17—N2	179.23 (9)
C2—C3—C4—O1	0.47 (12)	S1—C16—C17—N2	-3.09 (14)
C2—C3—C4—C5	-178.18 (12)	O5—N2—C17—C18	-77.67 (13)
C1—O1—C4—C3	-0.51 (12)	O6—N2—C17—C18	98.40 (12)
C1—O1—C4—C5	178.43 (10)	O5—N2—C17—C16	102.64 (12)
C3—C4—C5—C6	-75.12 (17)	O6—N2—C17—C16	-81.28 (13)
O1—C4—C5—C6	106.28 (12)	C16—C17—C18—C19	1.97 (16)
C4—C5—C6—C7	68.56 (14)	N2—C17—C18—C19	-177.71 (10)
C5—C6—C7—C8	-113.17 (15)	C17—C18—C19—C20	-1.50 (16)
C6—C7—C8—C9	4.3 (2)	C18—C19—C20—C21	-0.46 (17)
C7—C8—C9—C10	122.87 (14)	C19—C20—C21—C16	2.05 (16)
C8—C9—C10—C11	-168.60 (10)	C17—C16—C21—C20	-1.60 (15)
C9—C10—C11—C12	-168.75 (9)	S1—C16—C21—C20	-179.43 (8)
C13—N1—C12—C11	-58.04 (12)	O2—Si1—C24—C26	54.37 (8)
S1—N1—C12—C11	155.10 (8)	C23—Si1—C24—C26	172.91 (8)
C10—C11—C12—N1	-51.02 (12)	C22—Si1—C24—C26	-63.78 (9)
C12—N1—C13—C14	141.05 (9)	O2—Si1—C24—C25	-65.62 (9)
S1—N1—C13—C14	-73.52 (10)	C23—Si1—C24—C25	52.92 (10)
N1—C13—C14—C15	-158.29 (9)	C22—Si1—C24—C25	176.24 (9)
Si1—O2—C15—C2	122.96 (8)	O2—Si1—C24—C27	174.44 (8)
Si1—O2—C15—C14	-111.36 (8)	C23—Si1—C24—C27	-67.02 (9)
C1—C2—C15—O2	-2.96 (14)	C22—Si1—C24—C27	56.29 (10)

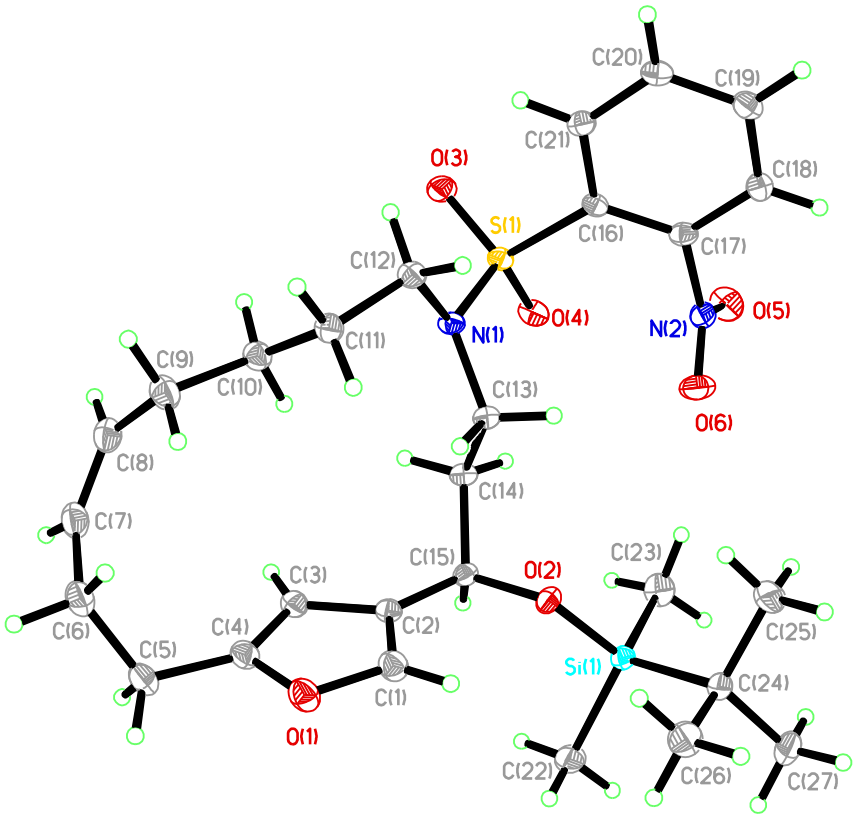


Figure 2. Perspective views showing 50% probability displacement ellipsoids

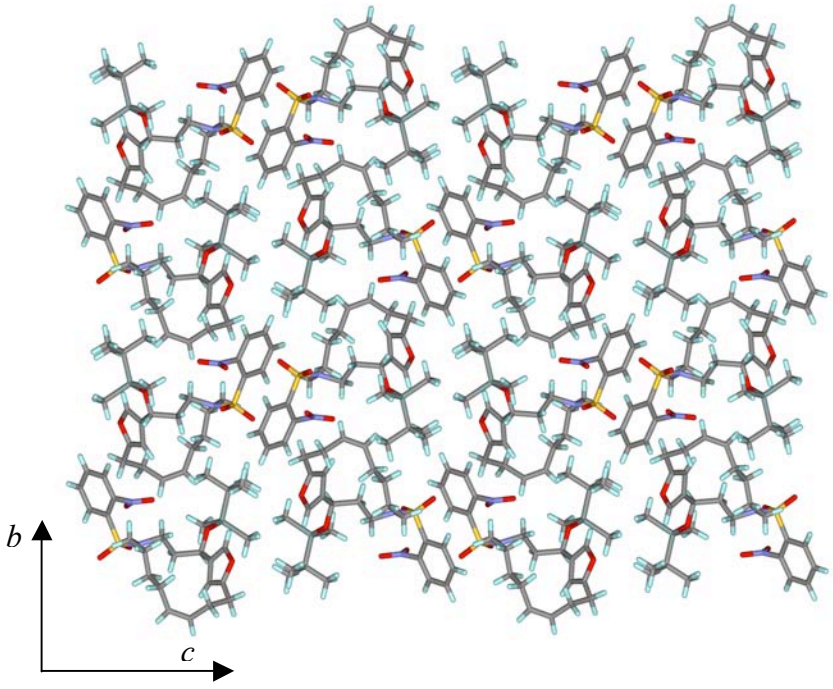
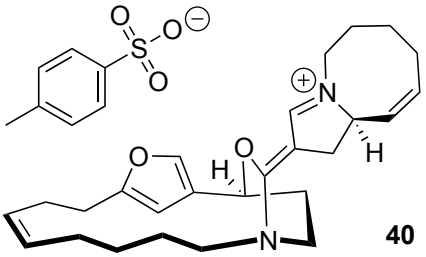


Figure 3. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

(*R*,2*Z*,9*Z*)-2-((1*S*,14*S*,*Z*)-4,16-dioxa-14-azatricyclo[12.2.2.1^{2,5}]nonadeca-2,5(19),8-trien-15-ylidene)-2,5,6,7,8,10a-hexahydro-1*H*-pyrrolo[1,2-*a*]azocin-4-ium 4-methylbenzenesulfonate (40)



40

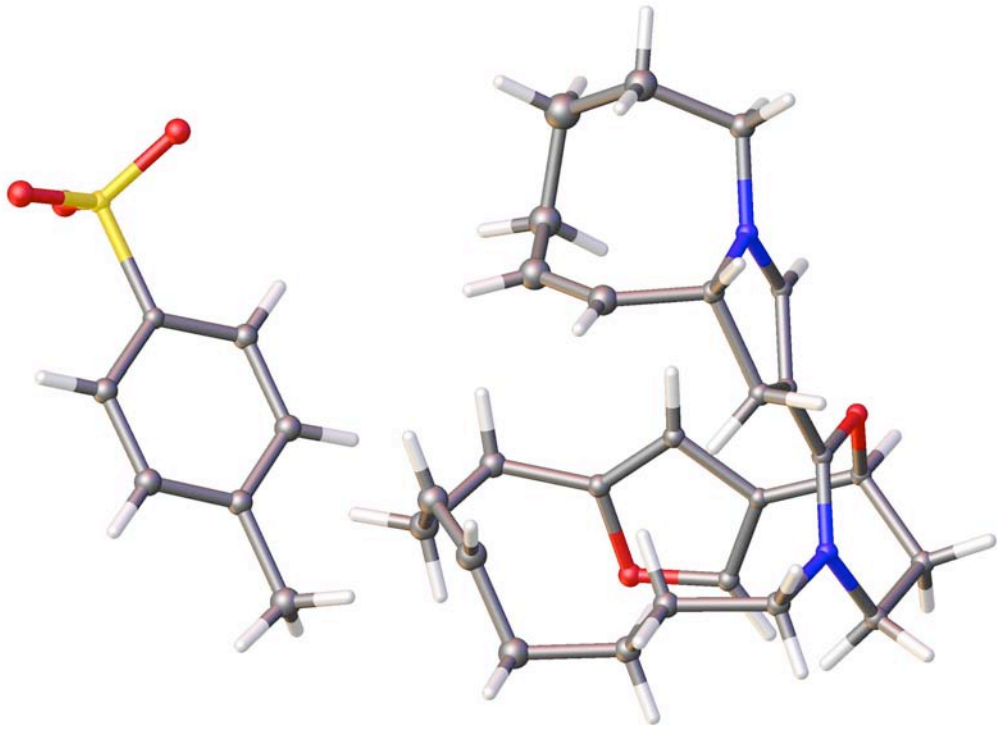


Figure 4. X-ray structure of **40**.

X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.78 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008) with OLEX 2 interface (Dolomanov, et al., 2009). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 3, and geometric parameters are shown in Table 4. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 3. Experimental details

	cbc003
Crystal data	
Chemical formula	$C_{33}H_{42}N_2O_5S$
M_r	578.75
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	8.3285 (3), 12.5911 (4), 28.403 (1)
V (Å^3)	2978.48 (18)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.15

Table 3 (Continued).

Crystal size (mm)	0.24 × 0.18 × 0.16
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.964, 0.976
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	102148, 6581, 6193
R_{int}	0.048
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.641
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.109, 1.07
No. of reflections	6581
No. of parameters	371
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.63, -0.29
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	-0.02 (7)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

Table 4. Geometric parameters (Å, º)

C27—C28	1.374 (3)	C10—H10	0.9500
C27—C32	1.388 (3)	C11—N2	1.331 (3)
C27—S58	1.781 (2)	C11—O1	1.350 (2)
C28—C29	1.387 (3)	C12—N2	1.482 (2)
C28—H28	0.9500	C12—C13	1.520 (3)
C29—C30	1.389 (3)	C12—H12A	0.9900
C29—H29	0.9500	C12—H12B	0.9900
C30—C31	1.388 (4)	C13—C14	1.510 (3)
C30—C33	1.509 (3)	C13—H13A	0.9900
C31—C32	1.392 (3)	C13—H13B	0.9900
C31—H31	0.9500	C14—O1	1.457 (2)

Table 4 (Continued).

C32—H32	0.9500	C14—C16	1.504 (3)
C33—H33A	0.9800	C14—H14	1.0000
C33—H33B	0.9800	C15—C16	1.350 (3)
C33—H33C	0.9800	C15—O2	1.370 (2)
O3—S58	1.4545 (17)	C15—H15	0.9500
O4—S58	1.4543 (16)	C16—C17	1.443 (3)
O5—S58	1.4571 (15)	C17—C18	1.345 (3)
C1—N1	1.465 (3)	C17—H17	0.9500
C1—C2	1.523 (4)	C18—O2	1.378 (2)
C1—H1A	0.9900	C18—C19	1.495 (3)
C1—H1B	0.9900	C19—C20	1.533 (3)
C2—C3	1.497 (5)	C19—H19A	0.9900
C2—H2A	0.9900	C19—H19B	0.9900
C2—H2B	0.9900	C20—C21	1.456 (4)
C3—C4	1.535 (5)	C20—H20A	0.9900
C3—H3A	0.9900	C20—H20B	0.9900
C3—H3B	0.9900	C21—C22	1.350 (4)
C4—C5	1.495 (4)	C21—H21	0.9500
C4—H4A	0.9900	C22—C23	1.465 (4)
C4—H4B	0.9900	C22—H22	0.9500
C5—C6	1.312 (4)	C23—C24	1.554 (4)
C5—H5	0.9500	C23—H23A	0.9900
C6—C7	1.509 (3)	C23—H23B	0.9900
C6—H6	0.9500	C24—C25	1.520 (3)
C7—N1	1.477 (2)	C24—H24A	0.9900
C7—C8	1.555 (3)	C24—H24B	0.9900
C7—H7	1.0000	C25—C26	1.534 (3)
C8—C9	1.521 (3)	C25—H25A	0.9900
C8—H8A	0.9900	C25—H25B	0.9900
C8—H8B	0.9900	C26—N2	1.474 (3)
C9—C10	1.395 (3)	C26—H26A	0.9900
C9—C11	1.403 (3)	C26—H26B	0.9900
C10—N1	1.318 (3)		
C28—C27—C32	119.93 (19)	N2—C12—C13	112.90 (17)
C28—C27—S58	119.15 (15)	N2—C12—H12A	109.0

Table 4 (Continued).

C32—C27—S58	120.92 (16)	C13—C12—H12A	109.0
C27—C28—C29	119.8 (2)	N2—C12—H12B	109.0
C27—C28—H28	120.1	C13—C12—H12B	109.0
C29—C28—H28	120.1	H12A—C12—H12B	107.8
C28—C29—C30	121.6 (2)	C14—C13—C12	109.11 (16)
C28—C29—H29	119.2	C14—C13—H13A	109.9
C30—C29—H29	119.2	C12—C13—H13A	109.9
C31—C30—C29	117.8 (2)	C14—C13—H13B	109.9
C31—C30—C33	121.6 (2)	C12—C13—H13B	109.9
C29—C30—C33	120.6 (2)	H13A—C13—H13B	108.3
C30—C31—C32	121.2 (2)	O1—C14—C16	110.13 (15)
C30—C31—H31	119.4	O1—C14—C13	106.85 (16)
C32—C31—H31	119.4	C16—C14—C13	114.71 (17)
C27—C32—C31	119.7 (2)	O1—C14—H14	108.3
C27—C32—H32	120.2	C16—C14—H14	108.3
C31—C32—H32	120.2	C13—C14—H14	108.3
C30—C33—H33A	109.5	C16—C15—O2	110.59 (17)
C30—C33—H33B	109.5	C16—C15—H15	124.7
H33A—C33—H33B	109.5	O2—C15—H15	124.7
C30—C33—H33C	109.5	C15—C16—C17	106.21 (17)
H33A—C33—H33C	109.5	C15—C16—C14	127.58 (18)
H33B—C33—H33C	109.5	C17—C16—C14	126.21 (18)
O4—S58—O3	113.14 (10)	C18—C17—C16	106.44 (18)
O4—S58—O5	113.10 (10)	C18—C17—H17	126.8
O3—S58—O5	113.11 (10)	C16—C17—H17	126.8
O4—S58—C27	105.60 (9)	C17—C18—O2	110.41 (18)
O3—S58—C27	105.82 (10)	C17—C18—C19	134.2 (2)
O5—S58—C27	105.12 (9)	O2—C18—C19	115.38 (18)
N1—C1—C2	114.06 (19)	C18—C19—C20	114.11 (19)
N1—C1—H1A	108.7	C18—C19—H19A	108.7
C2—C1—H1A	108.7	C20—C19—H19A	108.7
N1—C1—H1B	108.7	C18—C19—H19B	108.7
C2—C1—H1B	108.7	C20—C19—H19B	108.7
H1A—C1—H1B	107.6	H19A—C19—H19B	107.6
C3—C2—C1	116.0 (3)	C21—C20—C19	111.2 (2)
C3—C2—H2A	108.3	C21—C20—H20A	109.4

Table 4 (Continued).

C1—C2—H2A	108.3	C19—C20—H20A	109.4
C3—C2—H2B	108.3	C21—C20—H20B	109.4
C1—C2—H2B	108.3	C19—C20—H20B	109.4
H2A—C2—H2B	107.4	H20A—C20—H20B	108.0
C2—C3—C4	115.9 (2)	C22—C21—C20	127.4 (3)
C2—C3—H3A	108.3	C22—C21—H21	116.3
C4—C3—H3A	108.3	C20—C21—H21	116.3
C2—C3—H3B	108.3	C21—C22—C23	128.7 (3)
C4—C3—H3B	108.3	C21—C22—H22	115.7
H3A—C3—H3B	107.4	C23—C22—H22	115.7
C5—C4—C3	111.7 (3)	C22—C23—C24	111.6 (2)
C5—C4—H4A	109.3	C22—C23—H23A	109.3
C3—C4—H4A	109.3	C24—C23—H23A	109.3
C5—C4—H4B	109.3	C22—C23—H23B	109.3
C3—C4—H4B	109.3	C24—C23—H23B	109.3
H4A—C4—H4B	107.9	H23A—C23—H23B	108.0
C6—C5—C4	128.9 (2)	C25—C24—C23	113.5 (2)
C6—C5—H5	115.5	C25—C24—H24A	108.9
C4—C5—H5	115.5	C23—C24—H24A	108.9
C5—C6—C7	131.3 (2)	C25—C24—H24B	108.9
C5—C6—H6	114.3	C23—C24—H24B	108.9
C7—C6—H6	114.3	H24A—C24—H24B	107.7
N1—C7—C6	112.92 (18)	C24—C25—C26	114.52 (18)
N1—C7—C8	102.42 (16)	C24—C25—H25A	108.6
C6—C7—C8	111.00 (18)	C26—C25—H25A	108.6
N1—C7—H7	110.1	C24—C25—H25B	108.6
C6—C7—H7	110.1	C26—C25—H25B	108.6
C8—C7—H7	110.1	H25A—C25—H25B	107.6
C9—C8—C7	103.02 (16)	N2—C26—C25	113.27 (17)
C9—C8—H8A	111.2	N2—C26—H26A	108.9
C7—C8—H8A	111.2	C25—C26—H26A	108.9
C9—C8—H8B	111.2	N2—C26—H26B	108.9
C7—C8—H8B	111.2	C25—C26—H26B	108.9
H8A—C8—H8B	109.1	H26A—C26—H26B	107.7
C10—C9—C11	119.09 (18)	C10—N1—C1	125.16 (17)
C10—C9—C8	106.64 (17)	C10—N1—C7	111.36 (16)

Table 4 (Continued).

C11—C9—C8	133.73 (18)	C1—N1—C7	123.48 (17)
N1—C10—C9	113.04 (18)	C11—N2—C26	121.87 (16)
N1—C10—H10	123.5	C11—N2—C12	123.61 (17)
C9—C10—H10	123.5	C26—N2—C12	114.43 (16)
N2—C11—O1	119.22 (17)	C11—O1—C14	117.40 (15)
N2—C11—C9	127.39 (18)	C15—O2—C18	106.34 (15)
O1—C11—C9	113.37 (17)		
C32—C27—C28—C29	0.5 (3)	C13—C14—C16—C15	-27.6 (3)
S58—C27—C28—C29	-179.08 (18)	O1—C14—C16—C17	32.1 (3)
C27—C28—C29—C30	1.4 (4)	C13—C14—C16—C17	152.66 (19)
C28—C29—C30—C31	-2.2 (4)	C15—C16—C17—C18	0.3 (2)
C28—C29—C30—C33	176.5 (2)	C14—C16—C17—C18	-179.90 (18)
C29—C30—C31—C32	1.3 (4)	C16—C17—C18—O2	-0.3 (2)
C33—C30—C31—C32	-177.5 (2)	C16—C17—C18—C19	-178.9 (2)
C28—C27—C32—C31	-1.4 (3)	C17—C18—C19—C20	-110.5 (3)
S58—C27—C32—C31	178.16 (18)	O2—C18—C19—C20	70.8 (3)
C30—C31—C32—C27	0.5 (4)	C18—C19—C20—C21	68.1 (3)
C28—C27—S58—O4	76.95 (19)	C19—C20—C21—C22	-110.7 (3)
C32—C27—S58—O4	-102.60 (19)	C20—C21—C22—C23	0.7 (5)
C28—C27—S58—O3	-162.83 (17)	C21—C22—C23—C24	104.0 (3)
C32—C27—S58—O3	17.6 (2)	C22—C23—C24—C25	60.0 (3)
C28—C27—S58—O5	-42.9 (2)	C23—C24—C25—C26	177.72 (18)
C32—C27—S58—O5	137.57 (18)	C24—C25—C26—N2	57.4 (2)
N1—C1—C2—C3	-63.1 (3)	C9—C10—N1—C1	174.11 (19)
C1—C2—C3—C4	57.0 (4)	C9—C10—N1—C7	-5.9 (2)
C2—C3—C4—C5	49.3 (4)	C2—C1—N1—C10	126.6 (2)
C3—C4—C5—C6	-77.3 (4)	C2—C1—N1—C7	-53.4 (3)
C4—C5—C6—C7	-3.6 (5)	C6—C7—N1—C10	-103.9 (2)
C5—C6—C7—N1	8.6 (4)	C8—C7—N1—C10	15.5 (2)
C5—C6—C7—C8	-105.7 (3)	C6—C7—N1—C1	76.0 (2)
N1—C7—C8—C9	-18.1 (2)	C8—C7—N1—C1	-164.53 (18)
C6—C7—C8—C9	102.7 (2)	O1—C11—N2—C26	-171.06 (17)
C7—C8—C9—C10	15.7 (2)	C9—C11—N2—C26	10.2 (3)
C7—C8—C9—C11	-173.1 (2)	O1—C11—N2—C12	5.5 (3)
C11—C9—C10—N1	-179.60 (17)	C9—C11—N2—C12	-173.22 (19)

Table 4 (Continued).

C8—C9—C10—N1	-6.9 (2)	C25—C26—N2—C11	70.7 (2)
C10—C9—C11—N2	-175.89 (19)	C25—C26—N2—C12	-106.1 (2)
C8—C9—C11—N2	13.8 (4)	C13—C12—N2—C11	1.6 (3)
C10—C9—C11—O1	5.3 (3)	C13—C12—N2—C26	178.34 (17)
C8—C9—C11—O1	-165.0 (2)	N2—C11—O1—C14	24.1 (2)
N2—C12—C13—C14	-34.7 (2)	C9—C11—O1—C14	-157.02 (16)
C12—C13—C14—O1	60.1 (2)	C16—C14—O1—C11	67.9 (2)
C12—C13—C14—C16	-62.2 (2)	C13—C14—O1—C11	-57.3 (2)
O2—C15—C16—C17	-0.2 (2)	C16—C15—O2—C18	0.1 (2)
O2—C15—C16—C14	179.98 (17)	C17—C18—O2—C15	0.1 (2)
O1—C14—C16—C15	-148.13 (19)	C19—C18—O2—C15	179.07 (18)

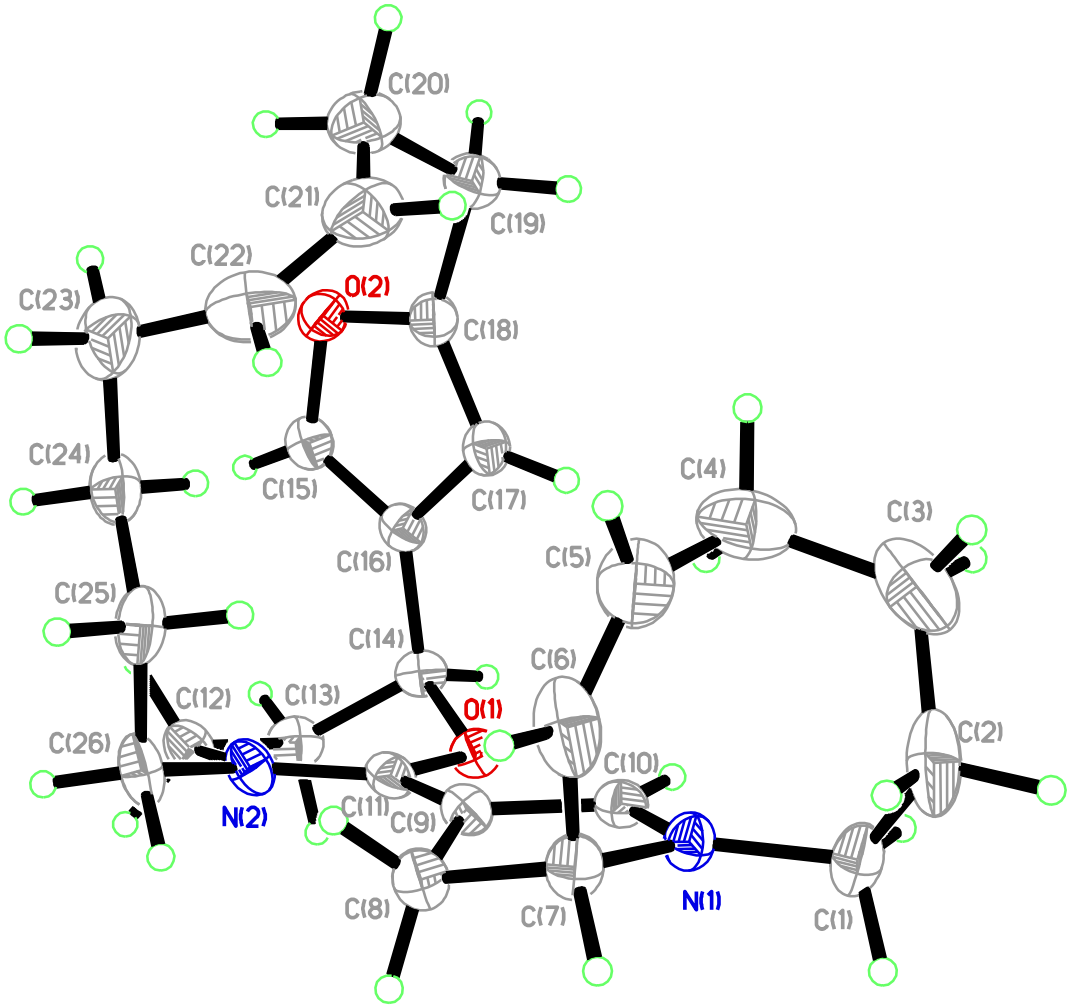


Figure 5. Perspective views showing 50% probability displacement.

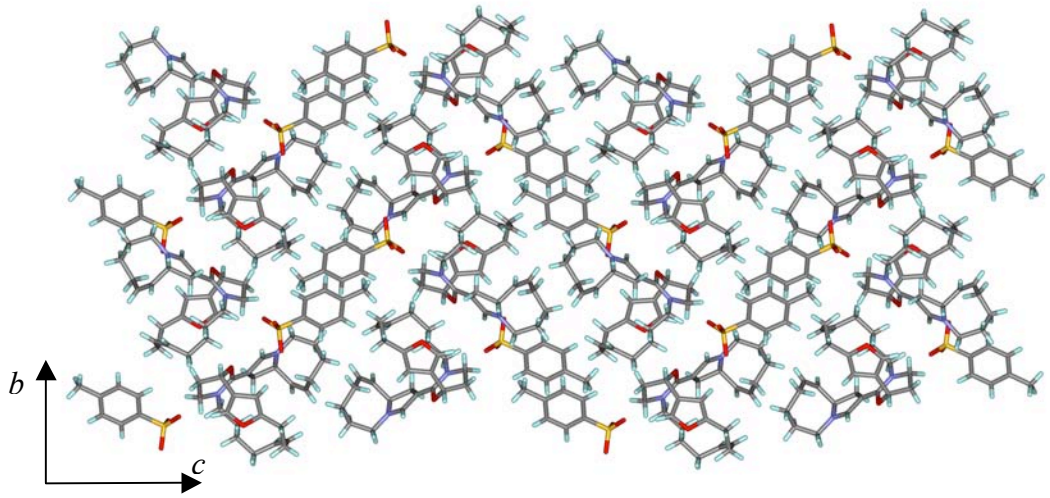
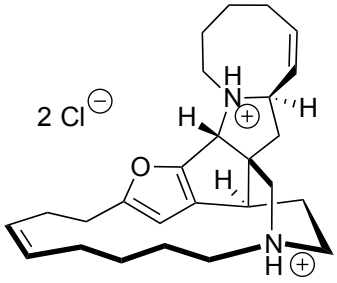


Figure 6. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

(−)-nakadomarin A•2HCl



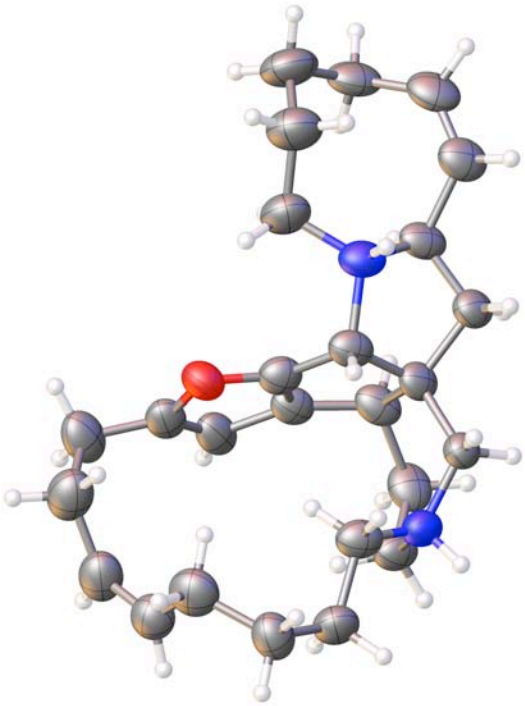


Figure 7. X-ray structure of (−)-nakadomarin A•2HCl.

X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 5, and geometric parameters are shown in Table 6. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 5. Experimental details

	cbc004
Crystal data	
Chemical formula	$C_{58}H_{92}Cl_4N_4O_4$
M_r	1051.25
Crystal system, space group	Triclinic, *P*1
Temperature (K)	100
a, *b*, *c* (Å)	9.1145 (2), 10.5842 (3), 19.4857 (6)
α, β, γ (°)	86.220 (2), 78.251 (2), 64.761 (2)
V (Å^3)	1664.24 (8)
Z	1

Table 5 (Continued).

Radiation type	Cu $K\alpha$
μ (mm^{-1})	1.93
Crystal size (mm)	0.14 × 0.08 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.774, 0.893
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	28211, 9146, 8461
R_{int}	0.054
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.596
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.112, 0.286, 1.09
No. of reflections	9146
No. of parameters	704
No. of restraints	93
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.91, -0.40
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.09 (3)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

Table 6. Geometric parameters (Å, º)

C3—N1	1.508 (14)	C33A—N3	1.51 (2)
C3—C4	1.512 (18)	C34A—C35	1.63 (3)
C4—C5	1.570 (18)	C35—C36	1.56 (2)
C2—C1	1.469 (14)	C36—C37	1.448 (16)
C2—N1	1.534 (12)	C37—C38	1.315 (16)
C2—C11	1.570 (14)	C38—C39	1.546 (14)
C1—C16	1.339 (14)	C39—N3	1.483 (13)
C1—O1	1.366 (12)	C39—C40	1.524 (15)
C5—C6	1.593 (19)	C40—C41	1.500 (13)

Table 6 (Continued).

C6—C7	1.500 (17)	C41—C42	1.510 (14)
C7—C8	1.315 (15)	C41—C45	1.584 (14)
C8—C9	1.545 (14)	C42—N4	1.511 (13)
C9—C10	1.428 (13)	C43—C44	1.524 (16)
C9—N1	1.535 (13)	C43—N4	1.549 (13)
C10—C11	1.547 (13)	C44—C45	1.462 (16)
C11—C12	1.501 (13)	C45—C46	1.557 (15)
C11—C15	1.555 (13)	C46—C47	1.398 (14)
C12—N2	1.481 (11)	C47—C48	1.324 (16)
C13—C14	1.501 (15)	C48—O2	1.394 (13)
C13—N2	1.549 (13)	C48—C49	1.508 (15)
C14—C15	1.560 (15)	C49—C50	1.553 (16)
C15—C16	1.491 (14)	C50—C51	1.487 (18)
C16—C17	1.435 (13)	C51—C52	1.311 (16)
C17—C18	1.353 (15)	C52—C53	1.559 (17)
C18—O1	1.367 (12)	C53—C54	1.493 (17)
C18—C19	1.446 (14)	C54—C55	1.540 (17)
C19—C20	1.506 (16)	C55—C56	1.523 (15)
C20—C21	1.517 (18)	C56—N4	1.470 (14)
C21—C22	1.374 (15)	C5S—C4S	1.31 (3)
C22—C23	1.457 (17)	C5S—C6S	1.36 (3)
C23—C24	1.547 (16)	C5S—O2S	1.37 (2)
C24—C25	1.538 (16)	C5T—C4T	1.35 (3)
C25—C26	1.520 (14)	C5T—O2T	1.37 (2)
C26—N2	1.477 (13)	C5T—C6T	1.37 (3)
C31—C46	1.353 (15)	C2S—O1S	1.40 (4)
C31—O2	1.374 (12)	C2S—C1S	1.49 (3)
C31—C32	1.464 (13)	C2S—C3S	1.50 (3)
C32—N3	1.549 (12)	C2T—C1T	1.34 (3)
C32—C41	1.558 (15)	C2T—C3T	1.37 (3)
C33—C34	1.47 (2)	C2T—O1T	1.38 (2)
C33—N3	1.512 (14)	C2P—C1P	1.32 (3)
C34—C35	1.61 (2)	C2P—C3P	1.36 (3)
C33A—C34A	1.48 (3)	C2P—O1P	1.37 (2)
N1—C3—C4	112.9 (11)	C36—C35—C34A	102.1 (18)

Table 6 (Continued).

C3—C4—C5	113.3 (13)	C34—C35—C34A	47.4 (17)
C1—C2—N1	114.5 (8)	C37—C36—C35	110.5 (11)
C1—C2—C11	100.9 (8)	C38—C37—C36	127.7 (10)
N1—C2—C11	105.5 (7)	C37—C38—C39	122.5 (10)
C16—C1—O1	113.0 (9)	N3—C39—C40	102.0 (8)
C16—C1—C2	116.2 (9)	N3—C39—C38	111.6 (9)
O1—C1—C2	130.7 (9)	C40—C39—C38	114.8 (9)
C4—C5—C6	114.7 (10)	C41—C40—C39	104.4 (8)
C7—C6—C5	109.3 (10)	C40—C41—C42	109.6 (8)
C8—C7—C6	126.5 (10)	C40—C41—C32	103.8 (8)
C7—C8—C9	124.7 (10)	C42—C41—C32	113.4 (8)
C10—C9—N1	103.2 (8)	C40—C41—C45	112.9 (8)
C10—C9—C8	117.4 (9)	C42—C41—C45	109.7 (9)
N1—C9—C8	111.2 (8)	C32—C41—C45	107.3 (7)
C9—C10—C11	106.7 (8)	C41—C42—N4	116.8 (8)
C12—C11—C10	110.8 (7)	C44—C43—N4	110.3 (8)
C12—C11—C15	110.7 (8)	C45—C44—C43	113.6 (10)
C10—C11—C15	113.2 (8)	C44—C45—C46	113.5 (9)
C12—C11—C2	113.2 (8)	C44—C45—C41	111.8 (9)
C10—C11—C2	101.7 (8)	C46—C45—C41	102.3 (8)
C15—C11—C2	106.8 (7)	C31—C46—C47	106.4 (10)
N2—C12—C11	117.5 (8)	C31—C46—C45	109.2 (9)
C14—C13—N2	112.5 (8)	C47—C46—C45	144.0 (11)
C13—C14—C15	111.9 (9)	C48—C47—C46	107.7 (10)
C16—C15—C11	103.5 (8)	C47—C48—O2	110.8 (9)
C16—C15—C14	113.5 (8)	C47—C48—C49	133.9 (11)
C11—C15—C14	111.5 (8)	O2—C48—C49	114.8 (10)
C1—C16—C17	104.8 (10)	C48—C49—C50	113.2 (9)
C1—C16—C15	110.5 (9)	C51—C50—C49	110.7 (11)
C17—C16—C15	144.2 (10)	C52—C51—C50	129.9 (13)
C18—C17—C16	106.5 (10)	C51—C52—C53	125.9 (12)
C17—C18—O1	111.1 (9)	C54—C53—C52	114.2 (11)
C17—C18—C19	134.2 (11)	C53—C54—C55	115.3 (10)
O1—C18—C19	114.5 (10)	C56—C55—C54	110.3 (10)
C18—C19—C20	113.5 (9)	N4—C56—C55	114.0 (9)
C19—C20—C21	112.6 (11)	C39—N3—C33	114.3 (10)

Table 6 (Continued).

C22—C21—C20	123.3 (13)	C39—N3—C33A	121 (2)
C21—C22—C23	129.9 (12)	C33—N3—C33A	22.1 (16)
C22—C23—C24	113.3 (11)	C39—N3—C32	106.1 (8)
C25—C24—C23	115.7 (9)	C33—N3—C32	111.3 (9)
C26—C25—C24	111.9 (10)	C33A—N3—C32	123 (3)
N2—C26—C25	112.4 (9)	C56—N4—C42	116.0 (8)
C3—N1—C2	113.5 (8)	C56—N4—C43	110.5 (8)
C3—N1—C9	116.5 (8)	C42—N4—C43	112.2 (8)
C2—N1—C9	105.7 (7)	C31—O2—C48	104.2 (8)
C26—N2—C12	115.3 (8)	C4S—C5S—C6S	112 (3)
C26—N2—C13	113.1 (8)	C4S—C5S—O2S	107 (2)
C12—N2—C13	111.7 (8)	C6S—C5S—O2S	116 (2)
C1—O1—C18	104.5 (8)	C4T—C5T—O2T	106 (2)
C46—C31—O2	110.8 (9)	C4T—C5T—C6T	114 (2)
C46—C31—C32	116.8 (10)	O2T—C5T—C6T	112 (2)
O2—C31—C32	131.9 (10)	O1S—C2S—C1S	109 (2)
C31—C32—N3	113.7 (8)	O1S—C2S—C3S	107 (3)
C31—C32—C41	102.7 (8)	C1S—C2S—C3S	108 (3)
N3—C32—C41	104.8 (8)	C1T—C2T—C3T	113 (3)
C34—C33—N3	110.8 (12)	C1T—C2T—O1T	106 (3)
C33—C34—C35	113.6 (14)	C3T—C2T—O1T	113 (3)
C34A—C33A—N3	119 (3)	C1P—C2P—C3P	110 (2)
C33A—C34A—C35	110 (3)	C1P—C2P—O1P	108 (2)
C36—C35—C34	113.6 (11)	C3P—C2P—O1P	112 (2)
N1—C3—C4—C5	107.9 (13)	C33—C34—C35—C34A	25 (2)
N1—C2—C1—C16	103.4 (10)	C33A—C34A—C35—C36	91 (3)
C11—C2—C1—C16	-9.4 (11)	C33A—C34A—C35—C34	-20.3 (17)
N1—C2—C1—O1	-82.4 (12)	C34—C35—C36—C37	-45.3 (16)
C11—C2—C1—O1	164.7 (9)	C34A—C35—C36—C37	-93.8 (18)
C3—C4—C5—C6	-59.4 (16)	C35—C36—C37—C38	86.3 (17)
C4—C5—C6—C7	-45.3 (14)	C36—C37—C38—C39	4 (2)
C5—C6—C7—C8	85.5 (14)	C37—C38—C39—N3	-87.2 (13)
C6—C7—C8—C9	7 (2)	C37—C38—C39—C40	157.4 (12)
C7—C8—C9—C10	155.8 (12)	N3—C39—C40—C41	44.3 (9)
C7—C8—C9—N1	-85.7 (13)	C38—C39—C40—C41	165.1 (9)

Table 6 (Continued).

N1—C9—C10—C11	42.6 (10)	C39—C40—C41—C42	-156.5 (9)
C8—C9—C10—C11	165.3 (9)	C39—C40—C41—C32	-35.0 (9)
C9—C10—C11—C12	-155.9 (9)	C39—C40—C41—C45	80.9 (10)
C9—C10—C11—C15	79.0 (11)	C31—C32—C41—C40	132.0 (8)
C9—C10—C11—C2	-35.3 (10)	N3—C32—C41—C40	13.0 (9)
C1—C2—C11—C12	-108.3 (8)	C31—C32—C41—C42	-109.1 (9)
N1—C2—C11—C12	132.2 (8)	N3—C32—C41—C42	131.9 (8)
C1—C2—C11—C10	132.7 (8)	C31—C32—C41—C45	12.3 (10)
N1—C2—C11—C10	13.3 (9)	N3—C32—C41—C45	-106.8 (8)
C1—C2—C11—C15	13.8 (9)	C40—C41—C42—N4	-168.7 (9)
N1—C2—C11—C15	-105.7 (8)	C32—C41—C42—N4	75.8 (11)
C10—C11—C12—N2	-169.9 (9)	C45—C41—C42—N4	-44.2 (12)
C15—C11—C12—N2	-43.4 (12)	N4—C43—C44—C45	-53.4 (12)
C2—C11—C12—N2	76.5 (11)	C43—C44—C45—C46	-54.8 (13)
N2—C13—C14—C15	-48.2 (12)	C43—C44—C45—C41	60.3 (12)
C12—C11—C15—C16	109.9 (9)	C40—C41—C45—C44	111.9 (11)
C10—C11—C15—C16	-124.9 (8)	C42—C41—C45—C44	-10.7 (12)
C2—C11—C15—C16	-13.8 (9)	C32—C41—C45—C44	-134.3 (9)
C12—C11—C15—C14	-12.4 (12)	C40—C41—C45—C46	-126.2 (9)
C10—C11—C15—C14	112.7 (10)	C42—C41—C45—C46	111.2 (9)
C2—C11—C15—C14	-136.1 (8)	C32—C41—C45—C46	-12.4 (10)
C13—C14—C15—C16	-58.1 (12)	O2—C31—C46—C47	1.2 (12)
C13—C14—C15—C11	58.3 (11)	C32—C31—C46—C47	174.2 (9)
O1—C1—C16—C17	-0.6 (11)	O2—C31—C46—C45	-173.3 (8)
C2—C1—C16—C17	174.6 (8)	C32—C31—C46—C45	-0.3 (13)
O1—C1—C16—C15	-174.4 (7)	C44—C45—C46—C31	128.7 (10)
C2—C1—C16—C15	0.8 (12)	C41—C45—C46—C31	8.1 (11)
C11—C15—C16—C1	8.4 (10)	C44—C45—C46—C47	-42 (2)
C14—C15—C16—C1	129.4 (9)	C41—C45—C46—C47	-162.9 (14)
C11—C15—C16—C17	-161.4 (12)	C31—C46—C47—C48	-0.4 (13)
C14—C15—C16—C17	-40.3 (17)	C45—C46—C47—C48	170.7 (14)
C1—C16—C17—C18	-0.7 (10)	C46—C47—C48—O2	-0.5 (13)
C15—C16—C17—C18	169.4 (12)	C46—C47—C48—C49	-171.1 (12)
C16—C17—C18—O1	1.8 (11)	C47—C48—C49—C50	112.1 (15)
C16—C17—C18—C19	-175.1 (10)	O2—C48—C49—C50	-58.3 (15)
C17—C18—C19—C20	112.3 (14)	C48—C49—C50—C51	-68.6 (14)

Table 6 (Continued).

O1—C18—C19—C20	-64.4 (14)	C49—C50—C51—C52	126.1 (13)
C18—C19—C20—C21	-67.6 (15)	C50—C51—C52—C53	-3 (2)
C19—C20—C21—C22	126.4 (12)	C51—C52—C53—C54	-156.9 (12)
C20—C21—C22—C23	-4.9 (19)	C52—C53—C54—C55	57.7 (15)
C21—C22—C23—C24	-153.0 (12)	C53—C54—C55—C56	63.2 (14)
C22—C23—C24—C25	60.9 (14)	C54—C55—C56—N4	176.9 (9)
C23—C24—C25—C26	60.6 (14)	C40—C39—N3—C33	-158.3 (9)
C24—C25—C26—N2	177.6 (9)	C38—C39—N3—C33	78.6 (11)
C4—C3—N1—C2	161.9 (10)	C40—C39—N3—C33A	178 (2)
C4—C3—N1—C9	-74.9 (13)	C38—C39—N3—C33A	55 (2)
C1—C2—N1—C3	29.7 (12)	C40—C39—N3—C32	-35.3 (9)
C11—C2—N1—C3	139.7 (9)	C38—C39—N3—C32	-158.4 (8)
C1—C2—N1—C9	-99.3 (10)	C34—C33—N3—C39	-78.1 (16)
C11—C2—N1—C9	10.8 (9)	C34—C33—N3—C33A	36 (7)
C10—C9—N1—C3	-160.0 (9)	C34—C33—N3—C32	161.7 (12)
C8—C9—N1—C3	73.3 (11)	C34A—C33A—N3—C39	40 (5)
C10—C9—N1—C2	-32.9 (9)	C34A—C33A—N3—C33	-37 (4)
C8—C9—N1—C2	-159.6 (8)	C34A—C33A—N3—C32	-101 (5)
C25—C26—N2—C12	-165.4 (8)	C31—C32—N3—C39	-97.2 (10)
C25—C26—N2—C13	64.3 (11)	C41—C32—N3—C39	14.2 (9)
C11—C12—N2—C26	-76.8 (11)	C31—C32—N3—C33	27.7 (14)
C11—C12—N2—C13	54.1 (12)	C41—C32—N3—C33	139.1 (10)
C14—C13—N2—C26	126.8 (9)	C31—C32—N3—C33A	49 (2)
C14—C13—N2—C12	-5.2 (12)	C41—C32—N3—C33A	160.4 (19)
C16—C1—O1—C18	1.6 (10)	C55—C56—N4—C42	-165.9 (9)
C2—C1—O1—C18	-172.7 (9)	C55—C56—N4—C43	64.9 (11)
C17—C18—O1—C1	-2.1 (10)	C41—C42—N4—C56	-77.3 (12)
C19—C18—O1—C1	175.4 (8)	C41—C42—N4—C43	51.0 (12)
C46—C31—C32—N3	104.9 (11)	C44—C43—N4—C56	129.5 (9)
O2—C31—C32—N3	-83.9 (13)	C44—C43—N4—C42	-1.7 (12)
C46—C31—C32—C41	-7.7 (12)	C46—C31—O2—C48	-1.5 (11)
O2—C31—C32—C41	163.4 (11)	C32—C31—O2—C48	-173.0 (11)
N3—C33—C34—C35	108.3 (16)	C47—C48—O2—C31	1.2 (12)
N3—C33A—C34A—C35	-100 (5)	C49—C48—O2—C31	173.8 (10)
C33—C34—C35—C36	-60.2 (17)		

Table 7. Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N1—H1···Cl3^{i}	0.93	2.15	3.048 (9)	163.2
N2—H2A···Cl2	0.93	2.05	2.975 (8)	174.8
N3—H3AA···Cl4^{ii}	0.93	2.15	3.049 (9)	161.6
N4—H4···Cl1^{iii}	0.93	2.05	2.977 (9)	174.7
O1S—H1S···Cl3^{i}	0.85	2.36	3.21 (2)	179.4
O1P—H1P···O1S	0.84	1.93	2.27 (3)	103.1
O2T—H2T···Cl4	0.85	2.32	3.171 (19)	179.5

Symmetry code(s): (i) *x*-1, *y*, *z*; (ii) *x*+1, *y*-1, *z*; (iii) *x*+1, *y*, *z*.

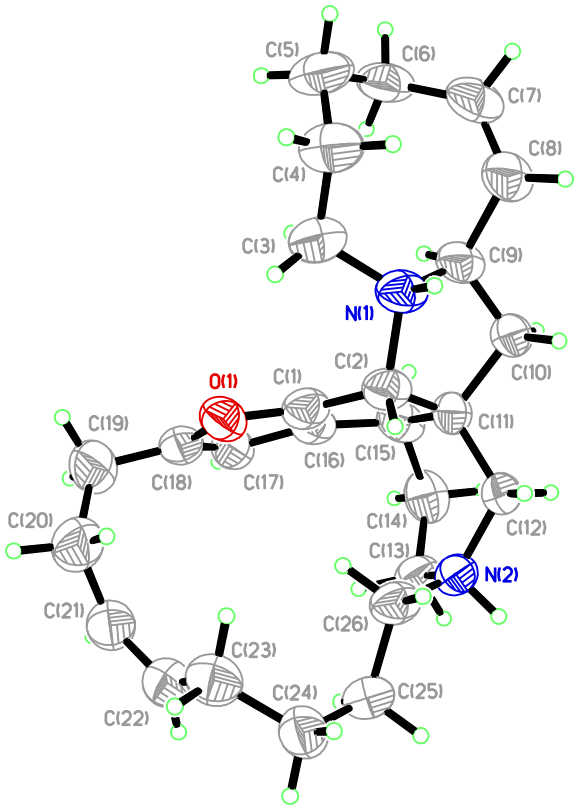


Figure 8. Perspective views showing 50% probability displacement.

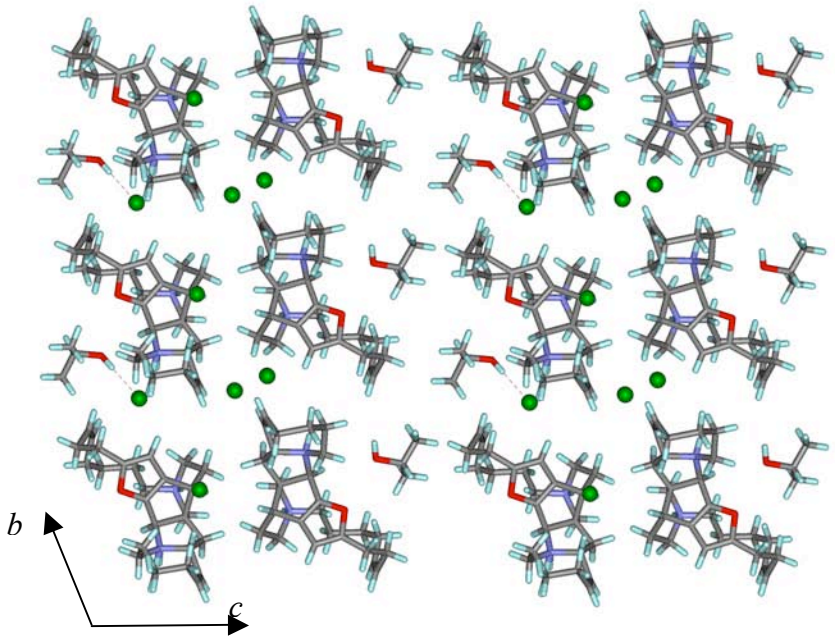


Figure 9. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

References:

[1] Bruker AXS APEX II, Bruker AXS, Madison, Wisconsin, 2009.
[2] Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., 2007.
[3] G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122.
[4] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann J. Appl. Cryst. 2009, 42, 339-341.